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Charles S. Shanahan IV

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**Efforts Towards the Total Synthesis of the Stemofoline Alkaloids
Utilizing a Novel 1,3-Dipolar Cycloaddition Reaction
and Application of the Pauson-Khand Reaction as a Novel Entry into
Bridged Azabicyclic Ring Systems**

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Charles S. Shanahan IV, Ph.D.

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Supervisor: Stephen F. Martin

A novel application of the Pauson-Khand reaction was applied to the synthesis of a series of bridged azatricyclic piperazines. This method represents the first application of the Pauson-Khand reaction to synthesize azabridged scaffolds. The ubiquity of bridged azabicyclic ring systems in biologically active natural product skeletons has provided the synthetic chemist with a wealth of opportunity for development over the last century. To this day, the development of new methodologies to tackle these structurally challenging systems remains at the forefront of synthetic chemistry.

During our efforts to achieve a total synthesis of the stemofoline alkaloids, we have thus far developed a novel and scalable synthetic strategy to access the fully functionalized caged azatricyclic core of these challenging alkaloids. The overall synthetic strategy we have implemented began with the commercially available and

affordable 2-deoxy-D-ribose as a chiral starting material. Furthermore, we have developed a novel 1,3-dipole cascade cycloaddition, which was successfully employed as the key step in the construction of the bridged azatricyclic core of the stemofoline alkaloids.

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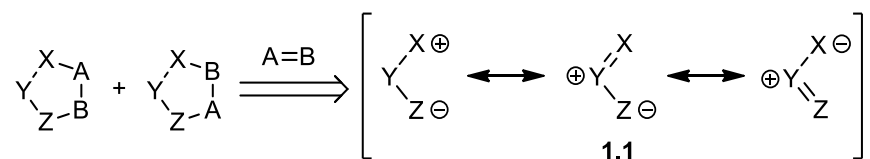
Chapter 1 – The Dipolar Cycloaddition Reactions of Azomethine Ylides and their Applications in Natural Product Total Synthesis

1.1 AZOMETHINE YLIDES AS USEFUL SYNTHONS IN THE PREPARATION OF HETEROCYCLES

1.1.1 Introduction

Few reaction classes are as ubiquitous in the heterocyclic field as the 1,3-dipolar cycloaddition (1,3-DPC). When the synthesis of 5-membered heterocyclic ring systems is required, no reaction has provided the synthetic chemist with a more expedient and versatile technique to construct these systems. From a retrosynthetic perspective, this class of reactions provides a well-studied and predictable synthon for designing the blueprint of complex heterocyclic targets (Scheme 1.1). The general structure of a 1,3-dipole **1.1** is a triatomic array that allows for a wide degree of elemental diversity (e.g. C, N, O, and S) at all three positions (X-Y-Z). Reactions of 1,3-dipoles with unsaturated compounds is a highly modular way to synthesize a plethora of 5-membered heterocyclic scaffolds with a great deal of elemental and stereodiversity.

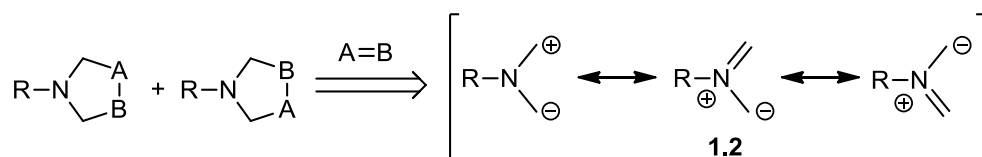
Scheme 1.1. Retrosynthetic Analysis of a 1,3-Dipolar Cycloaddition Reaction



Time and again the application of dipolar cycloadditions has proven productive in the synthesis of small heterocycles, and sufficiently general to tackle even the most demanding substrate configurations. Many reviews have been written regarding the

efficacy of 1,3-dipolar cycloadditions in the construction of pyrrolidine ring systems,¹ however a comprehensive review of the applications of azomethine ylides (AMY) as applied to complex natural product targets in particular is lacking in the literature. The azomethine ylide **1.2** is a very important class of 1,3-dipole inasmuch as the pyrrolidine ring systems resulting from the cycloadditions of these intermediates are highly prevalent in the structure of a vast array of naturally occurring alkaloids and biologically relevant molecules. The basic structure of the azomethine dipole is based on a C-N-C array, and when reacted with alkenes and alkynes give rise to pyrrolidine ring systems (Scheme 1.2).

Scheme 1.2. Retrosynthesis of Pyrrolidine-Like Ring Systems



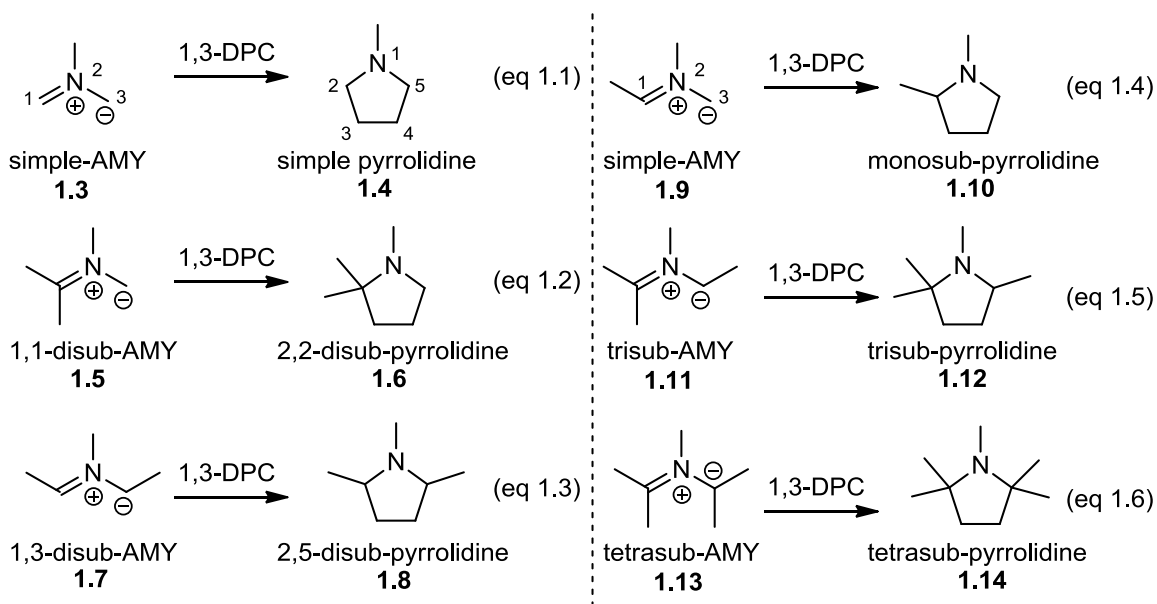
It is the aim of this review to study and survey the known applications of the azomethine ylide 1,3-dipolar cycloaddition to further advance the understanding of this powerful transformation in the context of complex molecule synthesis, and to help better equip the synthetic chemist for the successful implementation of this technology.

1.1.2 Azomethine Ylide Structure and Stereochemistry

When planning a synthesis around a 1,3-DPC of an azomethine ylide, one must first account for the substitution of the resulting pyrrolidine that will be required. In considering the 2,5-substitution of the target pyrrolidine, there are techniques to access just about any substitution pattern that can be conceived. There are six possible substitution patterns that azomethine ylides can possess, which translate directly into the

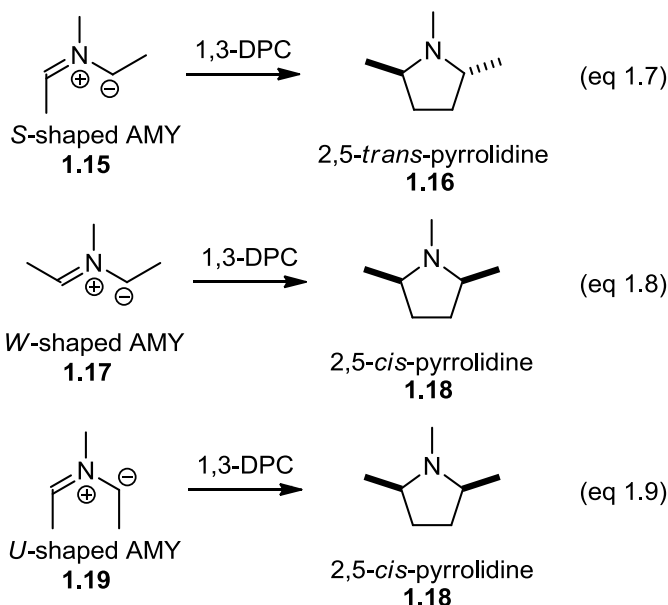
substitution patterns of the resulting pyrrolidine. Careful choice of the appropriate synthetic method is necessary to ensure that the azomethine ylide is generated with the desired substitution pattern and geometry. Outlined below (eq 1.1-1.5), are the different substitution patterns of azomethine ylides that can be accessed, the corresponding pyrrolidine systems that will result upon completion of a 1,3-DPC, as well as the establishment of a cursory nomenclature for these systems which will help with later discussion.

Scheme 1.3. Substitution Patterns of Azomethine Ylides & the Resulting Pyrrolidine Cycloadducts



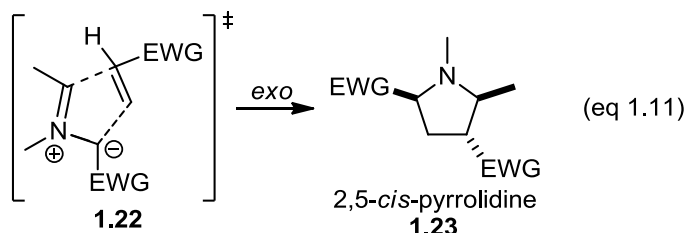
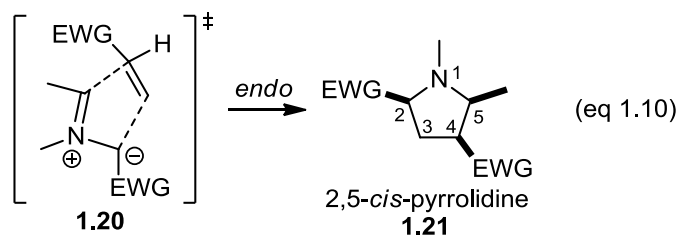
The 1,3-disubstituted azomethine ylides (**1.7**, eq 1.3) in particular are important because of their discrete and predictable geometric shapes that directly relate to the 2,5-stereochemistry that will result in the pyrrolidines after 1,3-DPC (eq 1.7-1.9). Depending on the synthetic method that is chosen for generating the target azomethine ylide,

different stereochemical outcomes will result as a consequence of the ylide geometry. The *trans*-ylide, known as the *S*-shaped ylide **1.15**, gives rise to the corresponding 2,5-*trans*-pyrrolidine **1.16** (eq 1.7). For the *cis*-ylides, however, both the *W*-shaped ylide **1.17** and *U*-shaped ylide **1.19**, will result in the 2,5-*cis*-pyrrolidines **1.18** (eq 1.8 & 1.9). Typically untethered azomethine ylides of this substitution pattern inherently favor the *S*-shaped geometry; however, the *W*-shaped ylide can form depending on the steric environment or the synthetic method chosen to generate the ylide. The *U*-shaped ylide **1.19** on the other hand is much less common, and typically reserved for cyclic ylides, which lead to bridged bicyclic structures. It is important to note that trisubstituted ylides (**1.11**, eq 1.5) and tetrasubstituted ylides (**1.13**, eq 1.6) can also be characterized as having *cis*- or *trans*-geometries, however these distinctions are typically harder to make.

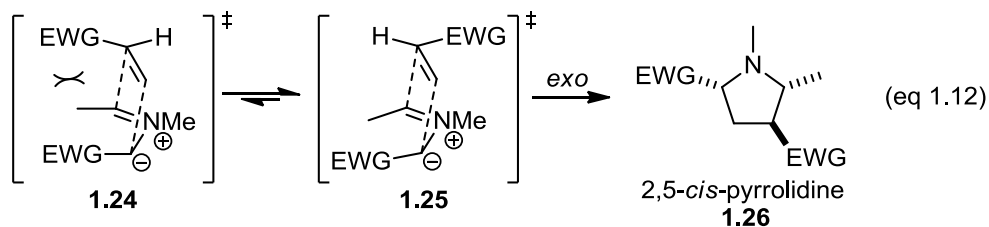


The consequence of *endo/exo*-selectivity in these reactions is another variable to consider in designing a synthetic plan, in that the substitution pattern and stereochemistry at the 3- and 4-positions of the resulting pyrrolidine product are a result of the alignment

of the dipolarophile relative to the azomethine ylide in the transition state. Fortunately, as with the geometry of the targeted azomethine ylide, the outcome tends to be predictable. In fact, the shape of the targeted ylide itself is often a determining factor in the reaction outcome with respect to *endo/exo*-selectivity (eq 1.10 & 1.11). As a rule of thumb, both *S*- and *W*-shaped ylides (**1.15** & **1.17**) tend to give high levels of *endo*-selectivity (via **1.20**) during the cycloaddition event; *S*-shaped systems, however, are more prone to deterioration in selectivity.



U-shaped ylides, which are much less common, tend to give high levels of *exo*-selectivity; presumably as a result of more sterically demanding *endo*-transition states such as **1.24** (eq 1.12).



Furthermore, the regiochemical outcomes of these cycloadditions are also highly predictable. With a polarized ylide such as **1.20** and **1.22** (eq 1.10 & 1.11), a majority of the electron density of the triatomic species will reside alpha to the electron withdrawing group. Thus, a cycloaddition with a polarized dipolarophile (such as acrylates) will occur to give a pyrrolidine ring with the substitution pattern represented by **1.21** and **1.23** (eq 1.10 & 1.11), where a carbon-carbon bond forms between the most electron-rich atom of the ylide and the most electron-poor β -atom of the dipolarophile.

1.1.3 Methods for the Generation of Azomethine Ylides Structures

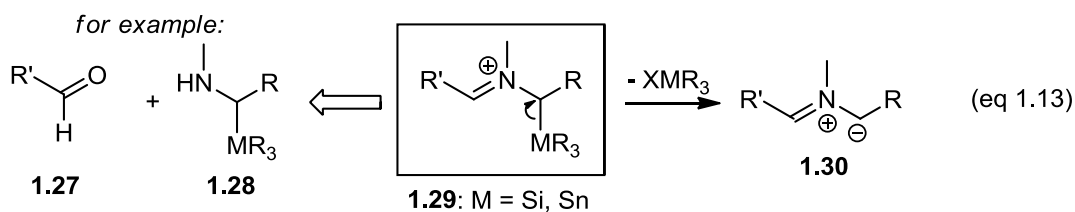
1.1.3.1 Introduction

The dipolar cycloaddition reactions of azomethine ylides have the potential to construct a vast amount of functional, positional, and stereodiversity into the synthesis of pyrrolidine ring systems, as described in the previous section; and, as a testament to the ubiquity of this ring system in organic chemistry, there has been an extensive set of unique methods developed in the literature for the generation of various types of azomethine ylide structures. These methods provide the synthetic chemist with a large toolbox to engineer a target-oriented synthesis utilizing this disconnect, as each method presents a choice of specific starting materials and reaction conditions that are often complimentary in addressing the unique concerns of any synthetic plan. The following subsections attempt to therefore establish a set of classifications that define the general strategies that have been used to generate the azomethine ylide synthon. In this way, the natural product total syntheses that are covered in this review can be segregated based on these classifications. For the most part, the formation of an iminium ion by some sort of condensation process is the first operation in generating an ylide. The condensation of

amines with aldehydes (via expulsion of a molecule of water) is a typical way to accomplish this; however, there are a number of different processes for preparing iminium ions in the literature. When an iminium ion is formed first, then the method will be classified by the proceeding mechanistic step that creates the azomethine ylide species directly. There are also methods that generate the azomethine directly from a neutral species, and typically these involve the manipulation and/or decomposition of heterocyclic species. Some methods are better suited for specific scenarios than others, so a general understanding of the options available is useful way to understand the synthetic design and context of the 1,3-DPC in each individual total synthesis.

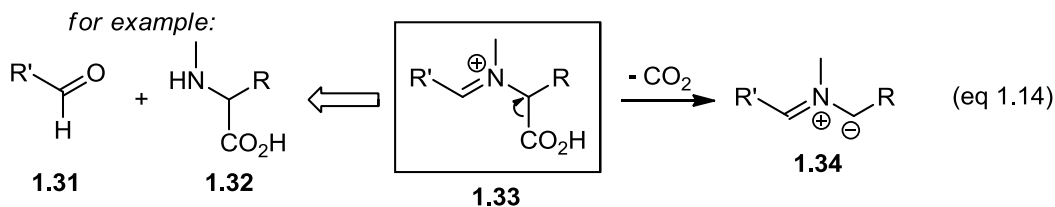
1.1.3.2 Methods Involving the Desilylation & Destannylation of Iminium Ion

A commonly employed method for the generation of azomethine ylides is the desilylation or destannylation of iminium ions of type **1.29** (eq 1.13). Treatment of such species with a nucleophile, typically fluoride ion, results in the azomethine ylide **1.30** and loss of the silyl- or stannousfluoride. The strength of the silicone-fluorine and tin-fluorine bonds drive this type of reaction, and often these reactions can be performed at mild temperatures, making them ideally suited for sensitive substrates. A typical set of starting materials for this process are α -aminosilanes or α -aminostannanes (such as **1.28**) and aldehydes. With respect to this type of method's application in total synthesis, a number of different substitution patterns have been accessed including simple-, mono-, and disubstituted ylides. A limiting factor to this strategy is that complex α -aminostannanes **1.28** required extra synthesis prior to the cycloaddition step, however, methods have been developed to accomplish this.



1.1.3.3 Methods Involving the Decarboxylation of Iminium Ions

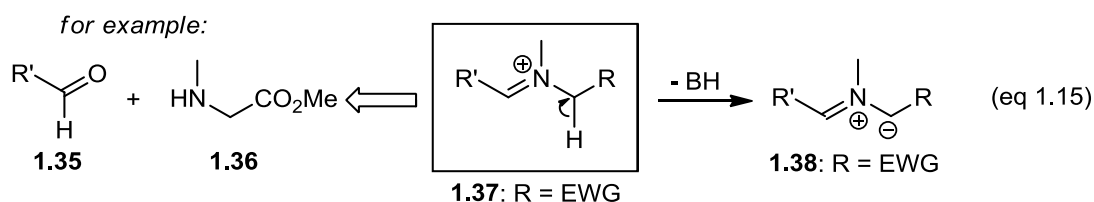
The decarboxylation of iminium ions such as **1.33** is probably the most fundamental method to generate azomethine ylides (eq 1.14). Typically the loss of carbon dioxide of the iminium ion requires elevated temperature; however, these reactions can be done at neutral pH providing them with an inherent benefit in some cases to the desilylation/destannylation techniques. The standard starting materials for this method are amino acid derivatives **1.32** and aldehydes. The applications of this type of method in the realm of natural products have only been used to access simple and mono-substituted azomethine ylides.



1.1.3.4 Methods Involving the Deprotonation of Iminium Ions

Another powerful method for generating azomethine ylides, and also the most commonly exploited tactic, is the deprotonation of iminium ions of type **1.37** (eq 1.15). In this type of system, the R-group must be an electron withdrawing group to increase the acidity of the α -proton. This type of azomethine ylide formation benefits from the availability of various different conditions that are known to effect the transformation. The reactions can be performed under mildly basic (typically with NEt_3), neutral, and

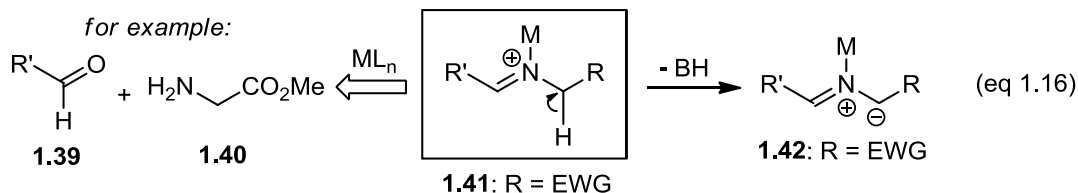
even acidic conditions (typically with sulfonic acid catalysts). Depending on the particular set of conditions chosen, the reactions can often be performed at mild temperatures, making this type of method ideally suited to general application. The typical starting materials for this transformation are aldehydes and N-substituted amino esters **1.36**, however, non-substituted amino esters have found limited use. This type of method is typically used to access higher substituted azomethine ylides, but most commonly the 1,3-disubstituted class. When N-substituted amino esters are used, the *S*-shape is generally preferred; on the other hand, non-substituted amino esters can be used to deliver the *W*-shaped ylide under certain conditions.



1.1.3.5 Methods Involving the Ionization of Metalloiminium Ions

The metallation of iminium ions sets up a number of different potential transformations to generate metallo-azomethine ylides of type **1.42** (eq 1.16). The only type of method for the ionization of metalloiminium ions that has found application in total synthesis, however, is the deprotonation of a metalloiminium ion of type **1.41**. While these methods are mechanistically similar to some of the other methods (*vide supra*), the metallation procedures deserve special consideration due to a number of unique factors. First, these methods allow access to non-nitrogen substituted pyrrolidine systems directly, whereas the other methods would require the use of N-alkyl substitution. Second, the typical ylide geometry that this method affords is the *W*-shaped ylide, which is harder to access with other similar methods. Finally, the use of a metal

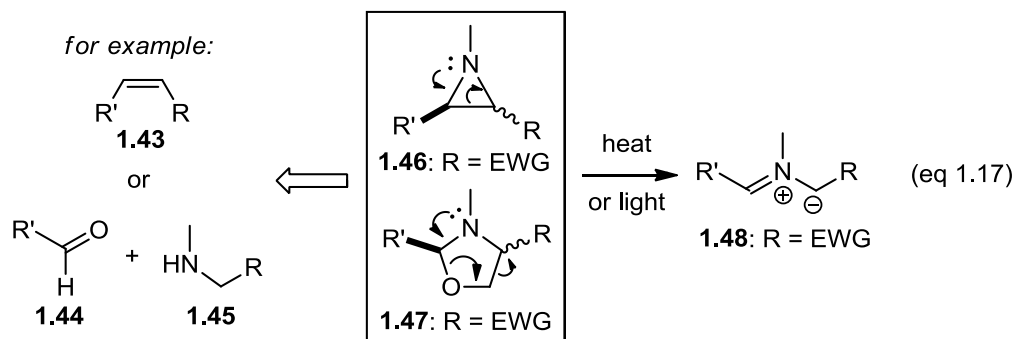
catalyst provides this class of reaction with the potential to be rendered catalytic asymmetric; in fact, a number of synthetic methods to that end have been reported in the literature (see Section 1.1.4 for further discussion of asymmetry in 1,3-DPC reactions of azomethine ylides). Depending on the tactic used to generate a metallo-azomethine ylide, the R-group can vary; however, for the more commonly employed tactic of iminium deprotonation, the R-group must be electron withdrawing. Thus the typical starting materials for this type of reaction are aldehydes and unsubstituted amino esters of type **1.40**. There is only one example of this type of transformation in total synthesis to access a *W*-shaped-1,3-disubstituted azomethine ylide, however the reaction was not performed in a catalytic asymmetric fashion, which still represents an area for potential development.



1.1.3.6 Methods Involving the Thermolysis/Photolysis of Heterocycles

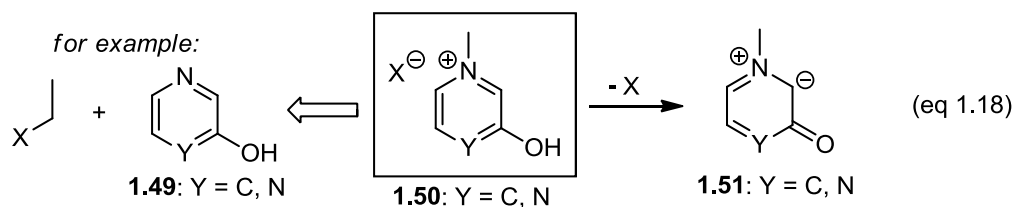
The thermolytic or photolytic decomposition of heterocyclic ring systems such as aziridines of type **1.46** and oxazolidines of type **1.47** represents another tactic for generating azomethine ylides that has attracted considerable attention in total synthesis (eq 1.17). One advantage of this type of method is that the azomethine ylide can be masked in the molecule and handled undisturbed until the targeted cycloaddition step. These types of heterocycles are relatively stable, and can withstand a number of different reaction conditions which allows the masked ylide function to be carried through a multistep sequence if desired. Also, the unmasking of the azomethine ylide from these

heterocycles does not require any added reagents, and can be generated under neutral pH by exposure to heat or light. There are a variety of methods for the generation of aziridines and oxazolidines, which makes choosing starting materials more challenging; however, the R-group in most cases must be an electron withdrawing group. The applications of these methods to natural product total synthesis have been used to access various mono- and disubstituted azomethine ylides.



1.1.3.7 Methods for the Generation of Conjugated Azomethine Ylides via Oxopyridinium & Oxopyrizinium Ions

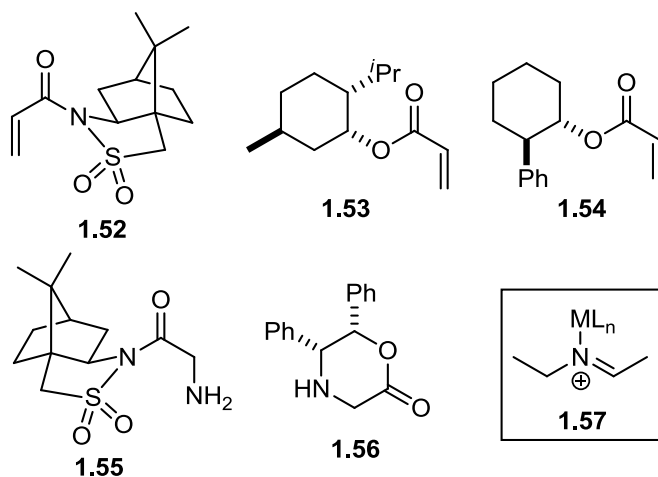
Conjugated azomethine ylides represent an important addition to the variety of tactics available for constructing pyrrolidine based heterocycles. One such method for generating these types of azomethine ylides is the deprotonation of oxopyridinium ions (1.50, where Y=C) and oxopyrizinium ions (1.50, where Y=N), which give rise to cyclic U-shaped azomethine ylides (eq 1.18). The generation of these types of stabilized ylides is generally very facile and can be done at ambient temperature; however, the cycloaddition event usually requires more energy. The product of dipolar cycloadditions of these types of ylides are bridged azabicyclic ring systems.



1.1.4 Common Tactics for Asymmetric Induction in 1,3-Dipolar Cycloadditions

The parameters for the induction of stereochemistry in the 1,3-DPC cycloaddition reactions of azomethine ylides can be defined in several ways. Intramolecular cycloadditions are the easiest systems to control in that the stereochemistry that results from the cycloaddition reaction is substrate dependent, and thus the chirality of the system must be built in prior to the cycloaddition event. Substrate control can also be highly effective in intermolecular examples for control of diastereoselectivity. The most common tactic for chiral induction in achiral systems is the employment of a chiral-auxiliary, which can be used to modify the dipolarophile or the azomethine ylide (Figure 1.1). The most commonly employed tactic is rendering the dipolarophile chiral (exemplified by **1.52**, **1.53** & **1.54**). Chiral amines such as **1.55** and **1.56**, however, have been used to generate chiral azomethine ylides by condensation with aldehydes.

Figure 1.1.



There are a other potential chiral auxiliaries that are not shown that can potentially serve these same purposes, but it should be noted that the Oppolzer sultam auxiliary (as in **1.52** & **1.55**) is the most frequently used auxiliary for 1,3-DPC applications. Typically when other auxiliaries were assayed, the Oppolzer auxiliary gave far and away the best overall results. The use of chiral azomethine ylides is less common, however, the Williams group has extensively developed the chiral amino acid derivative **1.56** as a general way to prepare *S*-shaped-1,3-disubstituted azomethine ylides. Finally, the potential for forming chiral metallo-azomethine ylides (such as **1.57**) using chiral metal catalysis serves as a potential area of development; however, there are no applications of this type of strategy to natural product total synthesis.

1.2 APPLICATIONS OF AZOMETHINE YLIDE 1,3-DIPOLAR CYCLOADDITION REACTIONS IN NATURAL PRODUCT TOTAL SYNTHESIS

1.2.1 Introduction

While there are many useful methods for the formation of azomethine ylides and many examples applications targeting unnatural heterocycles, it is the application of these technologies to the realm of natural product total synthesis that truly highlight the importance and versatility of the azomethine ylide synthon. The following review seeks to not only highlight these applications, but to characterize the syntheses in terms of the method that was used to generate the azomethine ylide itself. In this way we hope to fully illuminate this reaction as a general and truly unrivaled tactic for the preparation of the pyrrolidine ring systems. It is also important to put the cycloaddition reaction in the context of the total syntheses that they reside, by discussing the way the reaction was set-up and how the functionality of the cycloadduct itself was utilized going forward. As was described in the previous section, the various methods available allow for a great deal of diversity to be built into the ylide synthon by providing the synthetic chemist with a wide range of starting materials to design their syntheses around.

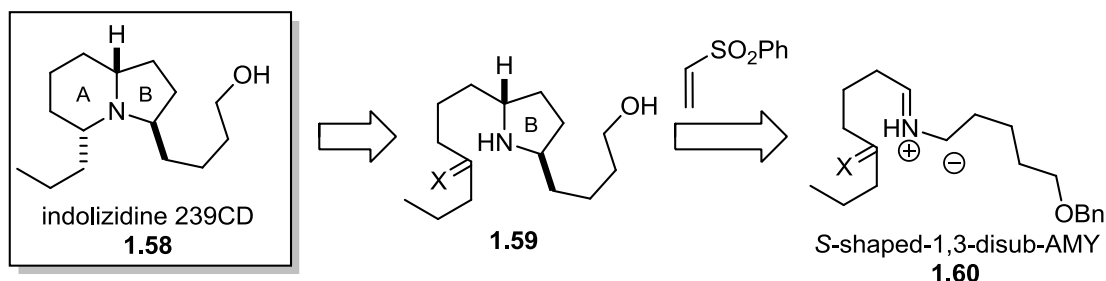
1.2.2 Applications Involving the Destannylation/Desilylation of Iminium Ions

1.2.2.1 Indolizidine 239CD

The alkaloid indolizidine 239CD (**1.58**, Scheme 1.4) belongs to a family of similar naturally occurring toxins, isolated from the poison frog *Dendrobates histrionicus*, which act as competitive blockers of neuromuscular transmission. A great example of the power of the azomethine ylide dipolar cycloaddition, comes out of the

Pearson synthesis of **1.58**.² He sought to employ a method developed in his group to form azomethine ylides via fluoride mediated destannylation of iminium ions, which has shown utility in generating diverse non-stabilized 1,3-substitued azomethine ylides.³ Applying this method, indolizidine 239CD was envisioned to come from a key dipolar cycloaddition of ylide **1.60** produced from a destannylation of an iminium ion (Scheme 1.4).

Scheme 1.4. Retrosynthesis of Indolizidine 239CD

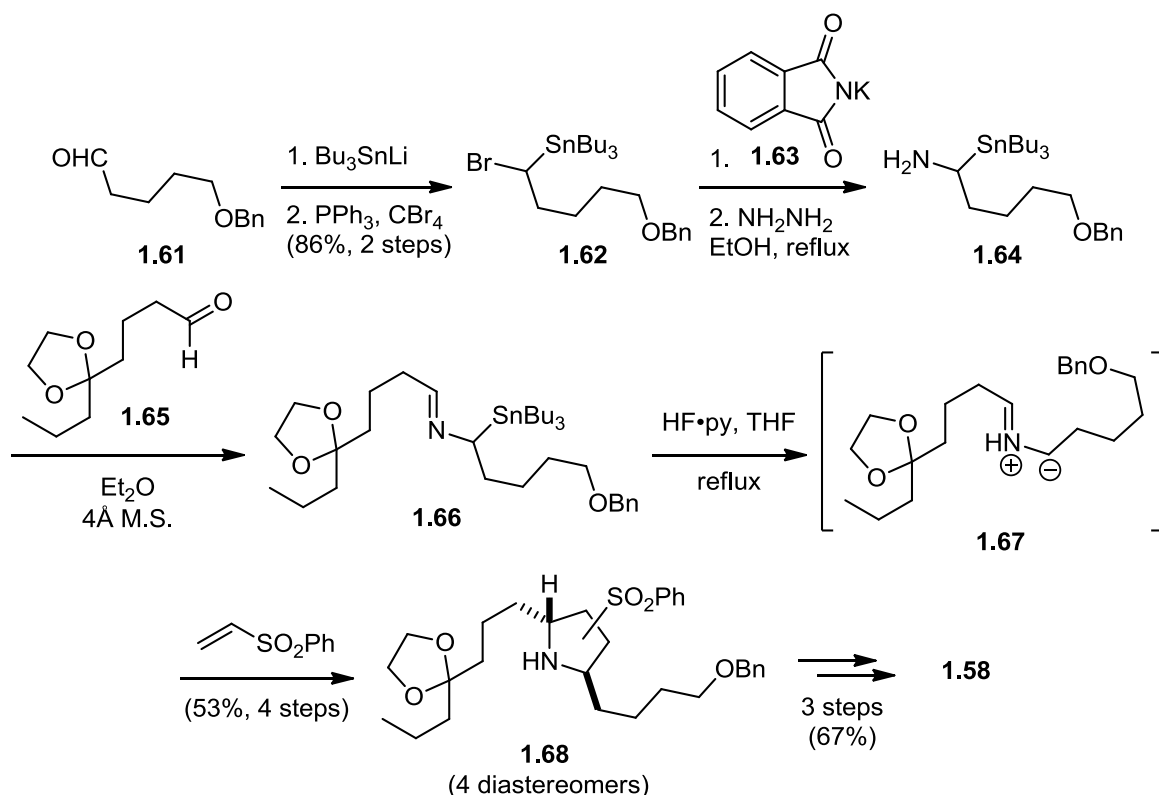


The cycloaddition step was set up by synthesizing two similarly sized fragments aldehyde **1.61** and α -aminostannane **1.62** (Scheme 1.5), bringing with them nearly all the total atoms in the final target minus the two provided by the dipolarophile. This highly convergent route commenced by addition of lithium tributyltin to commercially available aldehyde **1.61**, and conversion of the corresponding α -hydroxystannane to bromide **1.62** under Appel conditions in 86% yield. The requisite α -aminostannane fragment **1.64** was finally synthesized by nucleophilic displacement of the secondary bromide with K-phthalimide (**1.63**) and deprotection of the N-phthalimido moiety with hydrazine to give **1.64** in good overall yield. The aldehyde fragment **1.65**ⁱ was then condensed with α -aminostannane **1.64** to give imine **1.66**. This then set up the key cycloaddition reaction

ⁱ Synthesized in 5 steps from 6-hexenol in 39% overall yield.

whereupon imine **1.66** was heated with HF·pyridine to generate an azomethine ylide that underwent facile cycloaddition with phenyl vinyl sulfone to give pyrrolidine **1.68** as a mixture of four diastereomers in 53% yield. The lack of regioselectivity in this reaction is not surprising considering the non-stabilized nature of the azomethine ylide. With near symmetric substitution and no apparently electronic bias, the 1,3-resonance forms of this ylide should contribute equally to the overall structure and thus the reactivity of the azomethine ylide. The complete lack of *endo/exo*-selectivity, however, is harder to rationalize. Fortunately in this application the regio- and *endo/exo* selectivity were inconsequential, as the mixture of diastereomers converged to a single diastereomer when subjected to dissolving metal conditions, thus removing the sulfone stereocenter(s). The nonnegotiable 2,5-stereoselectivity, however, was excellent since the azomethine ylide reacted out of a discrete *S*-shaped ylide geometry to provide the desired 2,5-*anti* relationship in the pyrrolidine product. The synthesis of indolizidine 239CD was then finalized in three additional operations following the cycloaddition event to give **1.58** in 15 synthetic steps and in 11% overall yield.

Scheme 1.5. 1,3-DPC via Iminium Destannylation in Indolizidine 239CD Total Synthesis

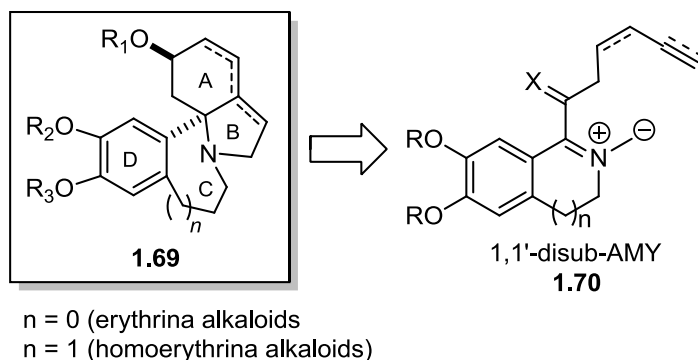


1.2.2.2 Erythrina & Homoerythrina Alkaloids

The erythrinane alkaloids constitute a large family of natural products, including the erythrina and homoerythrina alkaloids varying in the size of the C-ring (Scheme 1.6). These natural products exhibit a variety of interesting biological properties, including curare, sedative and hypotensive effects, as well as neuromuscular and CNS activities. Furthermore the unique, highly-fused azatetracyclic architecture has inspired a great deal of synthetic interest. Both Pearson and Livinghouse have developed strategies to construct the erythrina and homoerythrina core via comparable 1,3-dipolar cycloaddition

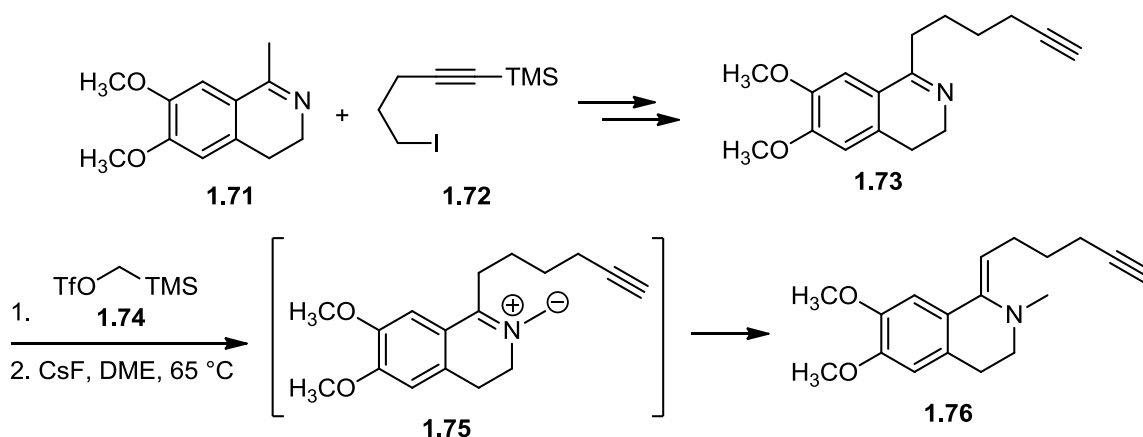
reactions of azomethine ylides such as **1.70** derived from both destannylation and desilylation of iminium ions.^{4, 5}

Scheme 1.6. Retrosynthesis of the Erythrina & Homoerythrina Alkaloids



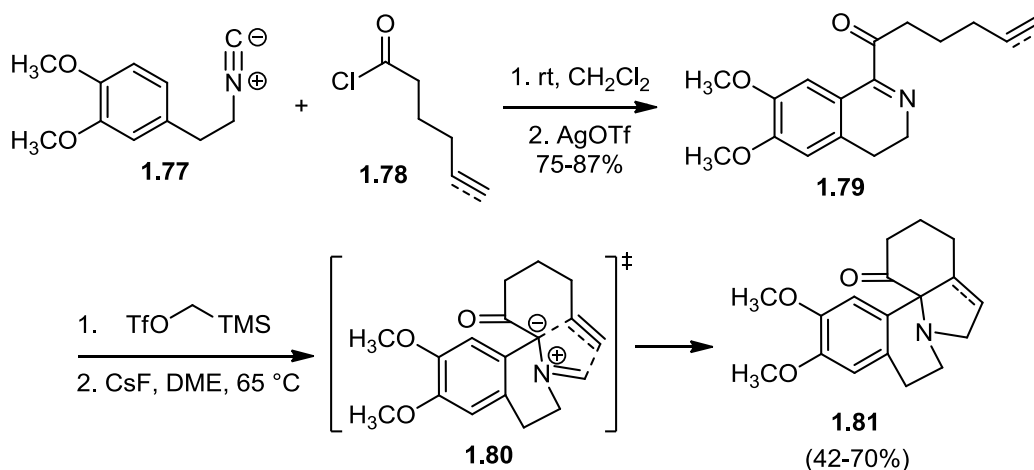
Livinghouse's work was published first in 1986, and involved a desilylation approach (Scheme 1.7).⁴ This strategy began with the alkylation of the metalloenamine derived from imine **1.71** with iodide **1.72** to give dihydroisoquinoline **1.73**. The cycloaddition method they targeted was earlier developed within their own group, which was applied to the much simpler natural products eserethole and deoxyeseroline.⁶ In the event, the alkylation of the imine with the reagent **1.74** gave an intermediate iminium ion. CsF was then introduced to effect the iminium desilylation, which provided azomethine ylide **1.75**, notably bearing acidic α -protons. These types of tautamerizable ylides are notoriously difficult to form and successfully employ in synthesis, and not surprisingly in this case, ylide **1.75** was rapidly quenched under the conditions of the reaction to form enamine **1.76** as the exclusive product.

Scheme 1.7. Livinghouse - 1,3-DPC Attempt on Substrate with Acidic α -Protons



In a subsequent iteration of his approach, Livinghouse synthesized a cycloaddition precursor with a fully substituted α -position not capable of tautomerization (Scheme 1.8). Two different acylimine substrates (**1.79**), varying in the saturation of the side chain, were synthesized by reaction of isonitrile **1.77** with an acid chloride of type **1.78**, followed by subsequent treatment with Lewis acid to facilitate the cyclization. Applying their cycloaddition chemistry to the erythrina core, this time with a more stable imine, the reaction successfully proceeded via alkylation/desilylation of imine **1.79** to give azomethine ylide **1.80**. This ylide then underwent an intramolecular cycloaddition with the tethered alkene or alkyne (depending on the substrate) to give the erythrina core **1.81** in moderate yields. The target natural product core would require unsaturation in the A or B ring of the natural product, which makes the alkyne substrate the more synthetically interesting example; in this case, however, the cycloaddition with the alkyne was the lower yielding of the two substrates tested. While this revision of the Livinghouse approach was an excellent improvement, the presence of the superfluous ketone moiety, which was required to stabilize the azomethine ylide, was less than optimal.

Scheme 1.8. Livinghouse - 1,3-DPC via Desilylation to Build Erythrina Core



A later attempt to access the homoerythrina core by Pearson in 2007 yielded an important extension of the cycloaddition approach to these types of molecules. Pearson aimed to apply his destannylation technology to these alkaloids similar to that which he used for indolizidine 239CD (*vide supra*). Cognizant of his method's suitability for forming and employing tautamerizable azomethine ylides, he turned his attention to the homoerythrina core intending to address one of the key deficiencies of the Livinghouse approach. A strategy was thus devised to unite fragments **1.82**ⁱⁱ and **1.83**ⁱⁱⁱ to form iodoketone **1.84** over a five step synthetic sequence. With all but one of the carbons present in the natural product core built into this compound, they next tested an expansion of their group's cycloaddition methodology. In the event, formation of an imine with α -aminostannane **1.85** set up an intramolecular alkylation to give a corresponding iminium ion. The liberated iodide anion then served to destannylate the iminium ion to give azomethine ylide **1.87**, which underwent cycloaddition with the appended vinyl sulfoxide. Furthermore, the vinyl sulfoxide product that was initially

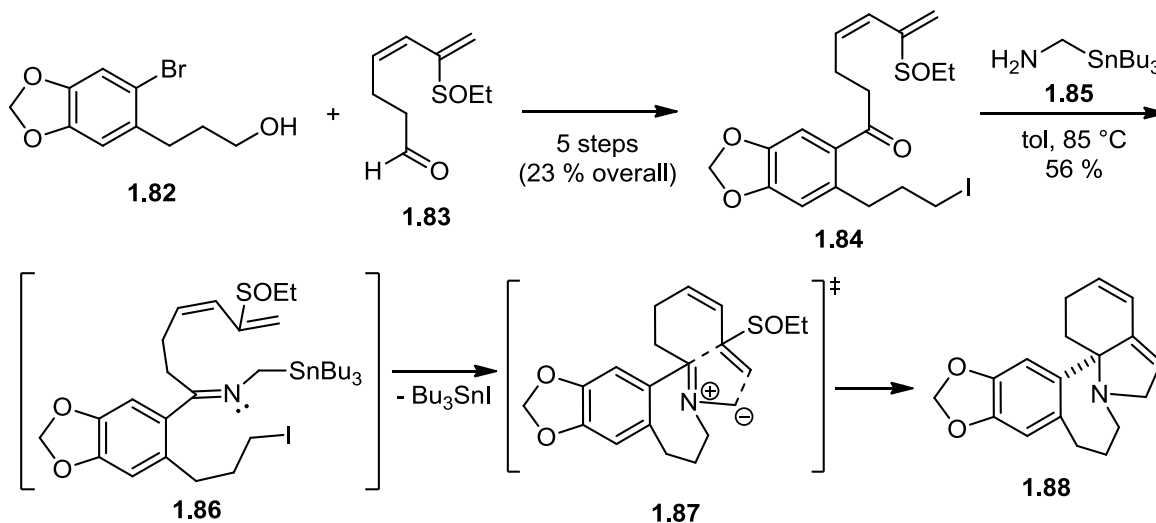
ⁱⁱ Synthesized in 2 steps from 6-bromopiperonal in ~80% overall yield.

ⁱⁱⁱ Synthesized in 4 steps from ethyl vinyl sulfide in 64% overall yield.

formed underwent spontaneous *syn*-elimination to give the homoerythrina core **1.88** in 12 synthetic steps in 7% overall yield from commercially available materials.

This impressive cascade reaction is unique in that the construction of the entire heterocyclic core was accomplished in one operation (See Sections 1.2.4.6 & 1.2.4.7 for discussion of similar cascade processes). Furthermore, the use of a vinyl sulfoxide as an alkyne surrogate could be a useful general tactic in controlling the regioselectivity of less selective cycloaddition reactions with alkynes.

Scheme 1.9. Pearson - 1,3-DPC via Destannylation to Build Homoerythrina Core

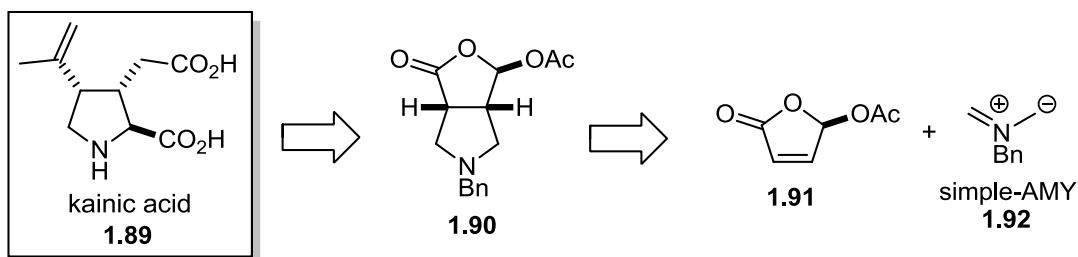


1.2.2.3 (-)-Kainic Acid

Kainic acid (**1.89**) has taken its place among some of the most highly studied natural products from both a biological and synthetic perspective. The CNS activities of this alkaloid in mammalian systems has made kainic acid an important tool in neuropharmacology since it can be used to stimulate nervous system functions; and has helped facilitate advancements in the understanding of diseases such as epilepsy,

Alzheimer's, and Huntington's disease by allowing researchers to administer kainic acid and mimic these types of disease states for further study. Efficient syntheses of kainic acid have become ever important because of the increasingly dwindling natural supply of this important compound. Since its first synthesis in 1979, kainic acid has succumb to dozens of total syntheses, allowing synthetic chemists to highlight a great deal of novel synthetic methods.⁷ Fukuyama envisioned kainic acid coming from bicyclic lactone **1.90**, which could be derived from a diastereoselective intermolecular 1,3-DPC of chiral dipolarophile **1.91** and simple azomethine ylide **1.92** (Scheme 1.10).

Scheme 1.10. Retrosynthesis of Kainic Acid

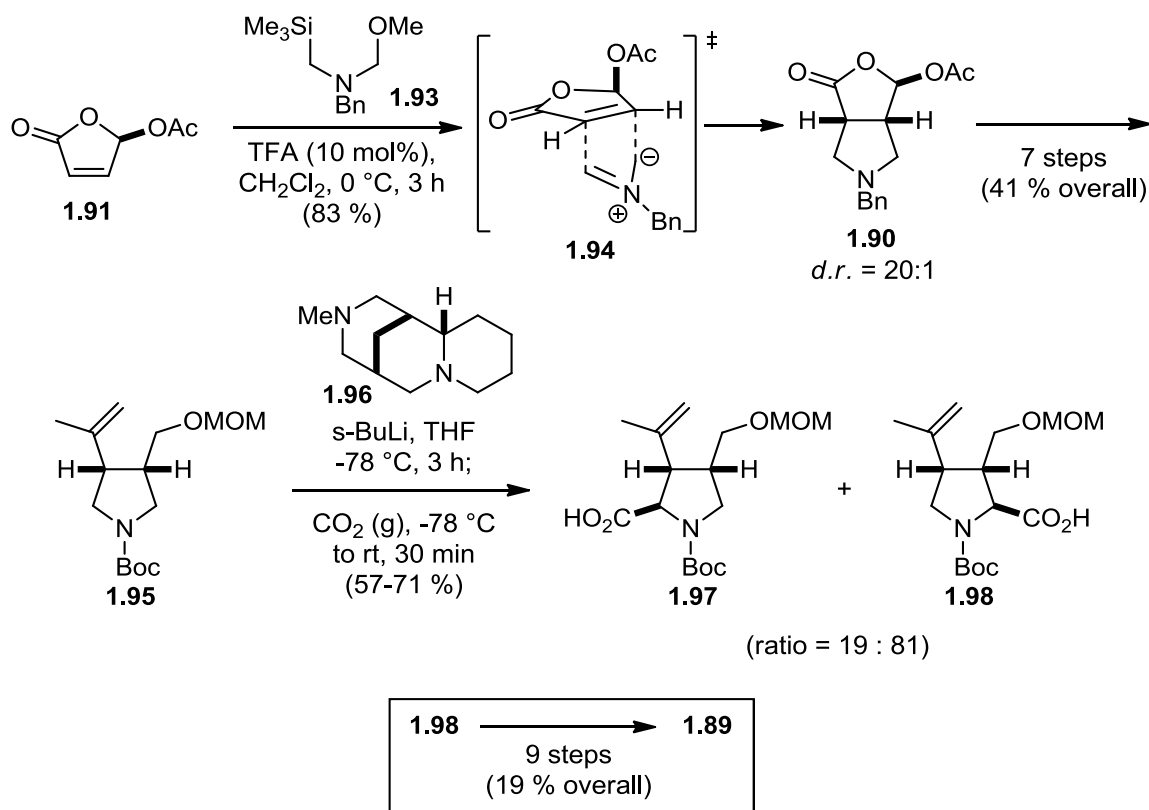


The Fukuyama synthesis of kainic acid employed an interesting intermolecular azomethine ylide cycloaddition via desilylation of an iminium ion derived from N,O-acetal **1.93** to give the simple azomethine ylide **1.92** (Scheme 1.11).^{7, 8, 9} The ylide reacted with dipolarophile **1.91**^{iv} via transition state **1.94** to give bicycle **1.90** as nearly a single diastereomer in 83% yield. Most notably, however, the chirality of the butenolide dipolarophile **1.91** had a profound effect on the stereochemistry of the cycloaddition reaction forcing the ylide to react on virtually only one face of the olefin. With pyrrolidine **1.90** in hand, Fukuyama carried this material through a 7 step sequence to access the refunctionalized **1.95**, in order to attempt an interesting α -lithiation reaction

^{iv} Synthesized in 2 steps from furfural using an enzymatic kinetic resolution in ~49% overall yield.

with (+)-sparteine surrogate **1.96**. This ligand controls the regio- and stereoselectivity of the initial deprotonation, and a subsequent reaction with carbon dioxide of the resulting organolithium species provided the fully functionalized kainic acid core **1.978** in moderate yields. An additional 9 steps provided (-)-kainic acid (**1.89**) so concluding a 20 step total synthesis in ~2% overall yield.

Scheme 1.11. 1,3-DPC via Iminium Desilylation to Kainic Acid Total Synthesis

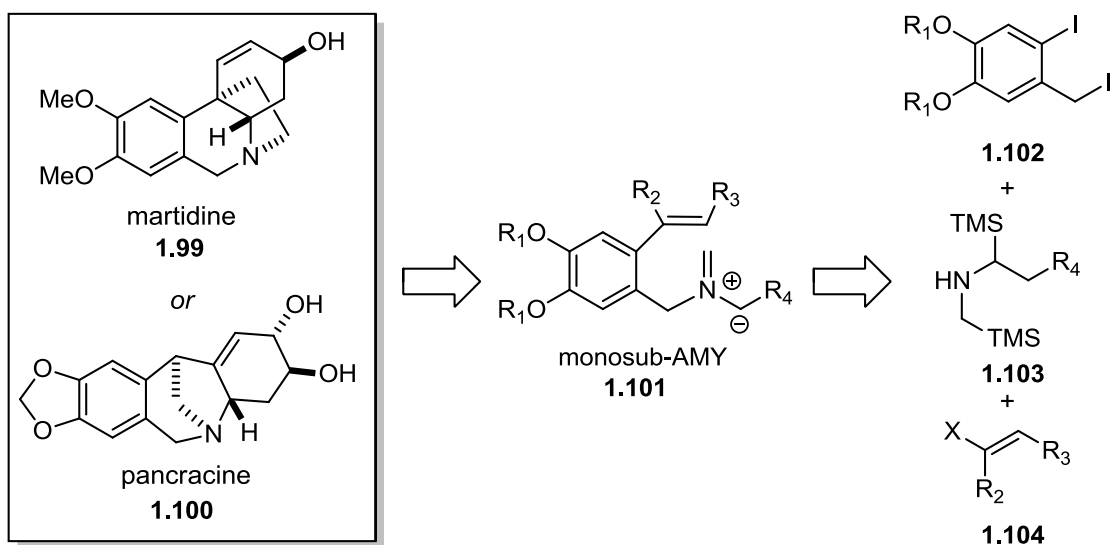


1.2.2.4 Amaryllidaceae Alkaloids

The amaryllidaceae alkaloids constitute a large class of interesting alkaloids of which the subclass crinine and montanine alkaloids reside. With the natural source of these alkaloids, the amaryllidaceae flowering plants, suffering a decline in population

because of habitat loss, the natural supply for these important alkaloids is quickly diminishing. Thus, a great deal of synthetic effort has been directed toward the synthesis of these valuable alkaloid natural products. The subclass of crinine alkaloids, exemplified by martidine (**1.99**, Scheme 1.12), consists of greater than 50 different alkaloids, mostly biologically active. Martidine exhibits interesting cytotoxic properties, and has served as a standard for the crinine class with respect to organic synthesis. The montanine subclass, exemplified by pancracine (**1.100**, Scheme 1.12), have shown anxiolytic, antidepressive, anticonvulsive, and hypotensive activities.

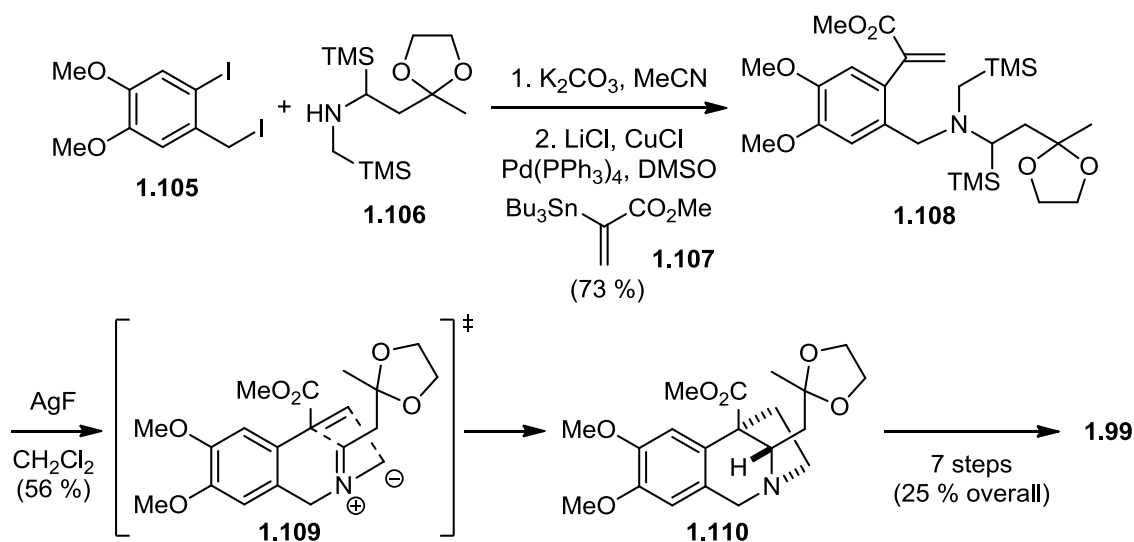
Scheme 1.12. Retrosyntheis of Amaryllidaceae Alkaloids



These structurally and biologically intriguing alkaloids have been the focus of extensive synthetic investigations, of which the efforts of Pandey have championed a general strategy using an azomethine ylide dipolar cycloaddition. Pandey developed a novel desilylative approach to azomethine ylides in 1993,¹⁰ and in extending this methodology has targeted azomethine ylides of type **1.101** as a general synthon for both

martidine and pancracine. The first synthesis of pancracine (**1.100**) was reported in 2005, which targeted a system where the R₃-substituent of the alkene dipolarophile (**1.108**) would be an electron withdrawing group to influence the cycloaddition's regioselectivity in favor of the pancracine skeleton (Scheme 1.12).¹¹ In 2009, he employed essentially the same tactic for martidine (**1.99**), but this time the R₂-substituent would bear the electron withdrawing group to enforce an inverted regioselectivity in the cycloaddition event to give the martidine core.¹²

Scheme 1.13. 1,3-DPC via Iminium Desilylation in Martidine Total Synthesis



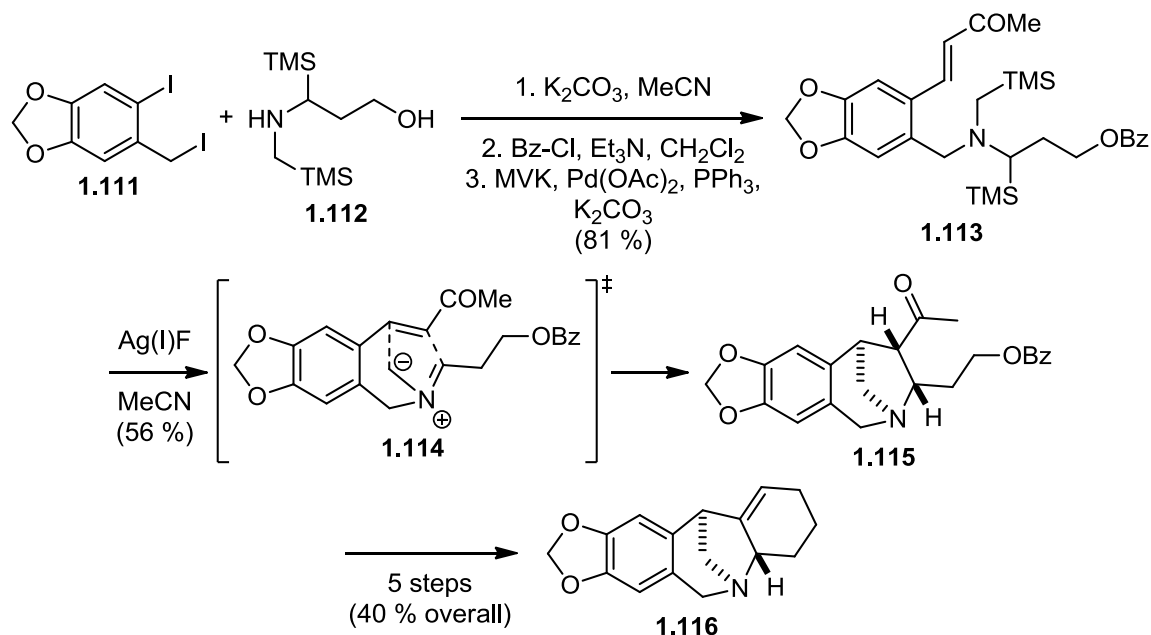
The synthesis of martidine (**1.99**) began with alkylation of bis-silylamine **1.106**^v with diiodide **1.105**,^{vi} followed by a Stille cross-coupling with vinyl stannane **1.107** to give cycloaddition precursor **1.108** in 73% yield (Scheme 1.13).¹² The strategy that Pandey employed for synthesizing this precursor is a general approach to N-alkyl-3-

^v Synthesized in a presumed ~7 steps from N-Boc-4-amino-2-butanol in ~35% overall yield, however specific details for each step were not provided. These data are derived from previously reported syntheses of similar compounds via similar synthetic strategies.

^{vi} Synthesized in two steps from 2-iodo-4,5-dimethoxybenzyl alcohol 78% overall yield.

substituted azomethine ylides, which his research group had previously developed. Any number of aminoalcohol starting materials, with a variety of substitution, can be quickly converted to bis-silylamines of type **1.103**, whereupon a subsequent alkylation to install a desired side chain provides diverse starting materials for azomethine ylides. In the case of martidine, the cycloaddition precursor **1.108**, when treated with two equivalents of Ag(I)F gave an azomethine ylide through a novel bis-desilylation reaction. The ylide reacted spontaneously with the tethered olefin via the described transition state **1.109** which aligns the more electron rich primary carbon of the azomethine ylide to react with the more electrophilic β -carbon of the enoate to give cycloadduct **1.110** in 56% yield. Seven more steps were then required to convert **1.110** into martidine, resulting in a ~17 step total synthesis in approximately 3% overall yield. Compound **1.111** was also applied to this exact same sequence in a later publication (substituting for **1.111** for **1.105**) to synthesize crinine, which amounts to the methylenedioxy version of martidine.

Scheme 1.14. 1,3-DPC via Iminium Desilylation in Pancracine Formal Synthesis



Following a nearly identical approach as the aforementioned martidine synthesis, Pandey also targeted a formal total synthesis of pancracine via the same disilylative azomethine ylide formation method (Scheme 1.14). The formal synthesis of pancracine (**1.100**) began with alkylation of bis-silylamine **1.112**^{vii} with diiodide **1.111**^{viii}, followed by a Heck cross-coupling with methyl vinyl ketone to give cycloaddition precursor **1.113** in 81% yield (Scheme 12).¹¹ Treatment of **1.113** with two equivalents of $Ag(I)F$ resulted in an azomethine ylide, which underwent intramolecular 1,3-DPC with the tethered enoate via transition state **1.114** to give the pancracine core **1.115** in 56%. Five additional steps were required to convert **1.115** into the tetracycle **1.116**, thus completing a formal total synthesis of pancracine in 16 steps and in 8% overall yield.

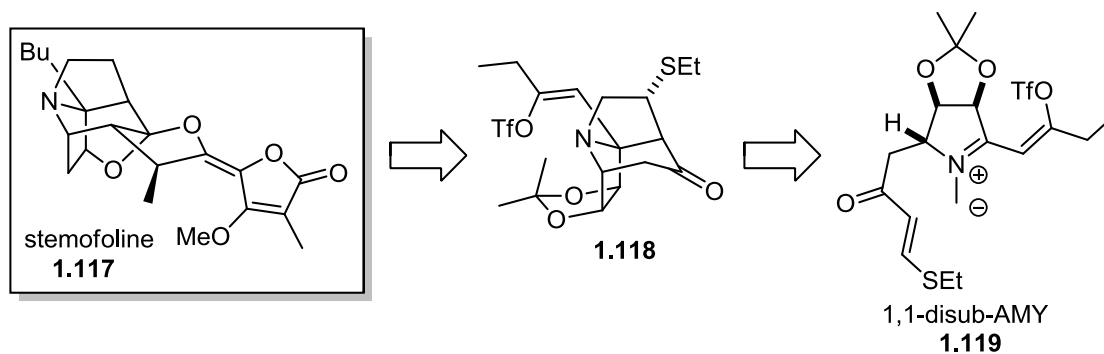
^{vii} Synthesized in 5 steps from 3-amino propanol in 57% overall yield.

^{viii} Synthesized in 2 steps from 6-Iodo-3,4-methylenedioxybenzyl alcohol in 78% overall yield.¹³ Reissig, H.-U.; Khan, F. A.; Czerwonka, R.; Dinesh, C. U.; Shaikh, A. L.; Zimmer, R. "Benzannulated Cyclooctanol Derivatives by Samarium Diiodide Induced Intramolecular Carbonyl-Alkene Coupling - Scope, Limitations, Stereoselectivity" *Eur. J. Org. Chem.* **2006**, 4419-4428.

1.2.2.5 Stemofoline Alkaloids

The stemofoline alkaloids, represented here by stemofoline (**1.117**, Scheme 1.15), comprise a very important part of the stemona family of natural products, named as such due to their isolation across a number of *Stemona* plant species. The roots and stems of these plants have long been used in traditional Asian medicine to treat symptoms associated with bronchitis and tuberculosis, and to also treat pest and lice infestations in both agricultural and human cases. The stemofoline alkaloids not only mirror the biological activity of the bulk plant, but also have shown anticancer activity. Additionally, these alkaloids present arguably the greatest synthetic challenge of all the stemona alkaloids owing to their dense caged hexacyclic architecture. These alkaloids have succumb to only two separate total syntheses, and recently Gin has reported progress toward these alkaloids aiming to apply an iminium desilylation to access azomethine ylide **1.119**, and thus the tricycle **1.118** upon intramolecular cycloaddition (Scheme 1.15).^{14, 15}

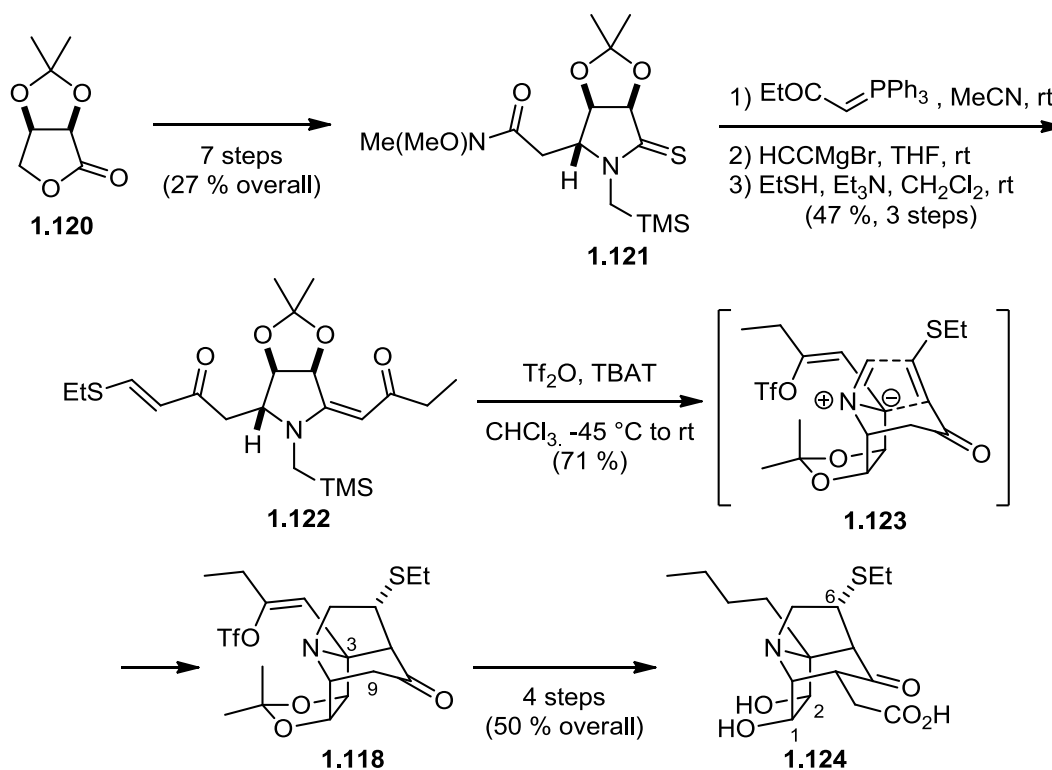
Scheme 1.15. Retrosynthesis of the Stemofoline Alkaloids



The Gin partial synthesis of stemofoline began with commercially available (-)-2,3-*O*-isopropylidene-D-erythrone (**1.120**), which was converted over a seven step

sequence to silyl thioamide **1.121** in 7 steps and 27% overall yield (Scheme 1.16). Next, a rapid assembly of the requisite functionality required for the targeted cycloaddition was performed, which included a Wittig olefination of thiolactam to install the vinylogous amide, addition of ethynyl Grignard to install the unsaturated side chain, and a final polarization of the ynone to give the vinylogous thioester **1.122** in 47% over the three step sequence. With the required functionality to generate the azomethine ylide and the appended dipolarophile installed, **1.122** was treated concurrently with triflic anhydride and tetrabutylammonium trifluorosilicate (TBAT), resulting in the formation of an azomethine ylide **1.119**, which reacted via transition state **1.123** with the tethered activated olefin to give the tricyclic core of stemofoline **1.118** in 71% yield. The tricyclic compound was then further elaborated to install and refunctionalize the C(3) and C(9) side chains to give **1.124** in 50% over a four step sequence. While a majority of the required functionality of stemofoline is accounted for in **1.124**, the challenge of selectively removing the thio-group at C(6) and the alcohol at C(1), while maintaining the C(2) alcohol, would have to be addressed. Additionally, a stereochemical inversion of the C(2) alcohol must also be performed. It is noteworthy, however, that the tricyclic core of these challenging alkaloids was accessed in asymmetric fashion in 15 total synthetic operation and in ~4% overall yield.

Scheme 1.16. 1,3-DPC via Iminium Desilylation in Stemofoline Partial Synthesis



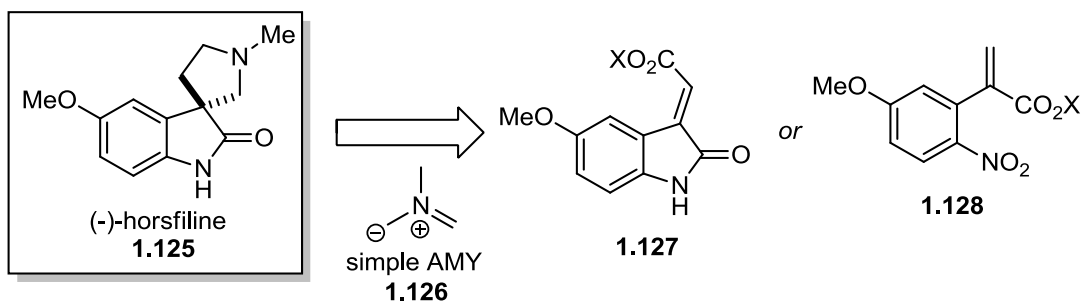
1.2.3 Applications Involving the Decarboxylation of Iminium Ions

1.2.3.1 (-)-Horsfiline

The vast family of spirooxindole type natural products has proven to be a classic set of targets for total synthesis. Additionally the 3,3'-pyrrolidinyI-spirooxindole subclass has proven to be a privileged scaffold in that most of the known natural products in this family exhibit anticancer activities. Horsfiline (**1.125**) represents one of the most structurally simple and fundamental of this class. There have been many synthetic approaches to horsfiline, including the efforts of Palmisano that probed the variables of an asymmetric intermolecular 1,3-DPC to install the spiropyrrolidine moiety (Scheme 1.17).^{16, 17} Two different approaches were studied which investigated the placement of a

chiral auxiliary on the dipolarophile in order to induce high asymmetry in an intermolecular 1,3-DPC with simple azomethine ylide **1.26**.

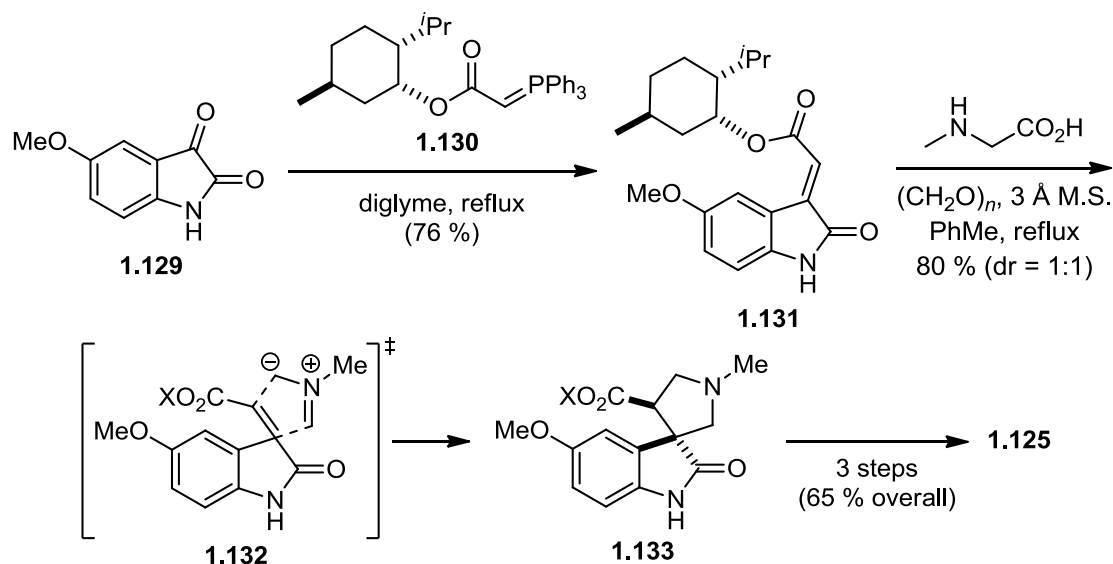
Scheme 1.17. Retrosynthesis of (-)-Horsfiline



Palmisano's first strategy was to perform the dipolar cycloaddition with the indole moiety intact.¹⁶ Starting with isatin derivative **1.129**, a Wittig olefination with chiral phosphorane **1.130**^{ix} delivered the chiral dipolarophile **1.131** in 76 % yield (Scheme 1.18). Dipolarophile **1.131** was then refluxed with paraformaldehyde and sarcosine resulting in a facile 1,3-DPC to give a mixture (1:1) of diastereomers **1.133** in 80% yield. While the cycloaddition itself worked in high yield, the menthyl derived auxiliary had no impact on the facial selectivity of the cycloaddition event. Several additional non-chiral derivatives of **1.131** were also reported and applied successfully to racemic syntheses of the horsfiline core. After separation of the diastereomers of **1.133**, the synthesis of (-)-horsfiline was completed in three additional steps to give **1.125** in 7 total synthetic steps ~20% overall yield.

^{ix} Synthesized in two steps from menthol and bromoacetic acid in an undisclosed overall yield.

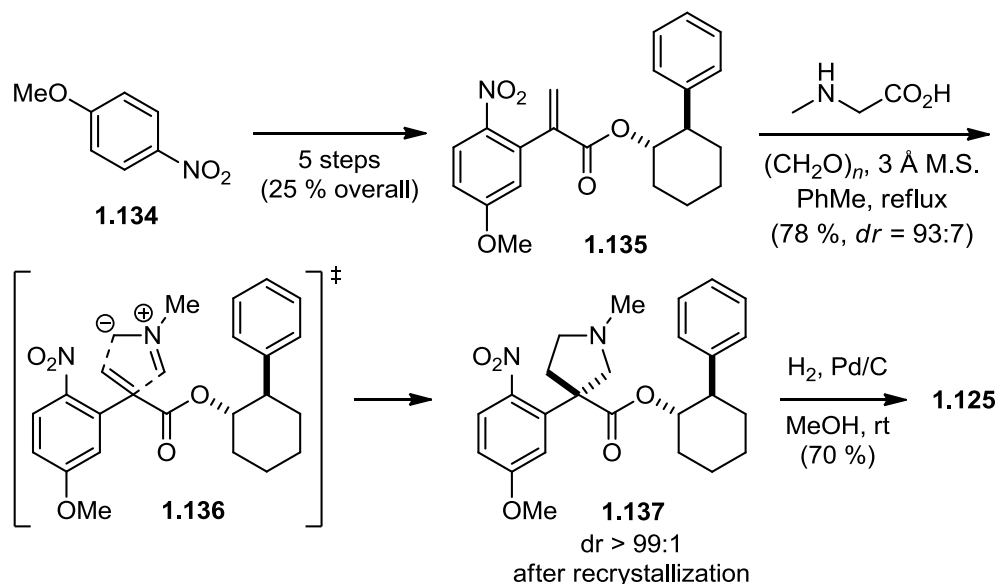
Scheme 1.18. 1,3-DPC via Iminium Decarboxylation in Horsfiline Total Synthesis



While the first approach did provide horsfiline in enantiomerically pure form, the efficacy of the 1,3-DPC was less than desired. In a second attempt to construct the horsfiline core with an asymmetric 1,3-DPC, Palmisano turned his attention to chiral dipolarophile **1.135**, which could be accessed in five steps and 25% overall yield from *p*-nitroanisole (**1.134**, Scheme 1.19).¹⁷ The cycloaddition was then performed with paraformaldehyde and sarcosine to give pyrrolidine **1.137** in 78% as a mixture (93:7) of diastereomers, which was enhanced to >99:1 after a single recrystallization. The total synthesis was completed by hydrogenolysis of the nitro moiety, resulting in concomitant cyclization to give **1.125** in 7 total synthetic steps in ~13% overall yield. It is interesting to note that by moving the chiral auxiliary closer to the aryl group and thus performing the cycloaddition on a 1,1-disubstituted olefin provided a very significant enhancement in stereoselectivity of the 1,3-DPC event. It is also important to note that a number of chiral auxiliaries were screened and that the 2-phenyl-2-cyclohexanol auxiliary used in **1.135** gave the best diastereoselectivity as well as the most favorable mobility on silica gel

during purification. Unfortunately, the overall yield of this approach was lower than the first generation approach due to the inefficiency of their synthesis of dipolarophile **1.135**.

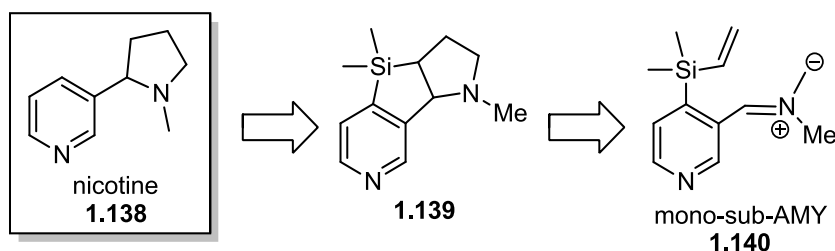
Scheme 1.19. 1,3-DPC via Iminium Decarboxylation in Horsfiline Total Synthesis



1.2.3.2 Nicotine

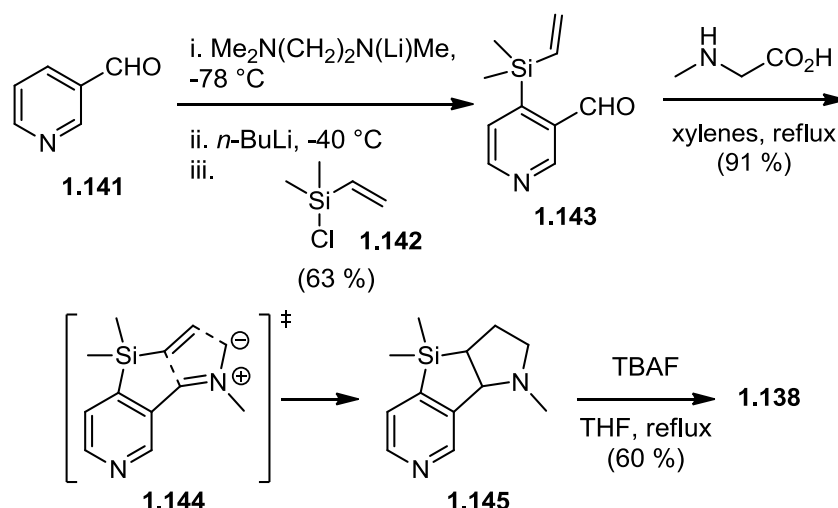
The alkaloid nicotine (**1.138**) needs no introduction with respect to its role in society. In medicine, nicotine and its analogues have been investigated as medicines to treat disorders such as Alzheimer's, Parkinson's, and Tourette's diseases. The synthesis of nicotine has been reported a number of times since its first synthesis in 1904; however, there is one synthesis of the pyrrolidine ring using a 1,3-DPC. Bashiardes reported an intriguing 1,3-DPC, wherein a silicone tether was employed to facilitate an intramolecular cycloaddition of a mono-substituted azomethine ylide (**1.140**, Scheme 1.20) with an unactivated olefin to give tricycle **1.139**. A cascade desilylation of **1.139** would then deliver nicotine.¹⁸

Scheme 1.20. Retrosynthesis of Nicotine



The approach to nicotine began with an *ortho*-lithiation reaction of nicotinaldehyde (**1.141**) followed by silylation with vinyltrimethylsilyl chloride (**1.142**) to give aldehyde **1.143** in 63% yield (Scheme 1.21). Next, by heating with sarcosine in refluxing xylenes, an iminium decarboxylation gave azomethine ylide, which reacted via the cycloaddition transition state **1.144** to furnish pyrrolidine **1.145** in 91% yield. A global desilylation with TBAF gave nicotine (**1.138**) in a short three step sequence in 35% overall yield. Also important to note, is that the Bashiardes approach also was useful in making a small library of nicotine analogues by the same approach. This tactic represents an interesting strategy for facilitating a cycloaddition with an unactivated olefin. A common approach to simple pyrrolidines would generally require the use of vinyl sulfones, which typically give a mixture of diastereomers that can all be converged on to the desired product by desulfurization (see section 1.3.2.1 for an example). While the Bashiardes approach is not necessarily more efficient, it provides a complimentary stratagem to simple pyrrolidines by 1,3-DPC.

Scheme 1.21. 1,3-DPC via Iminium Decarboxylation in Nicotine Total Synthesis

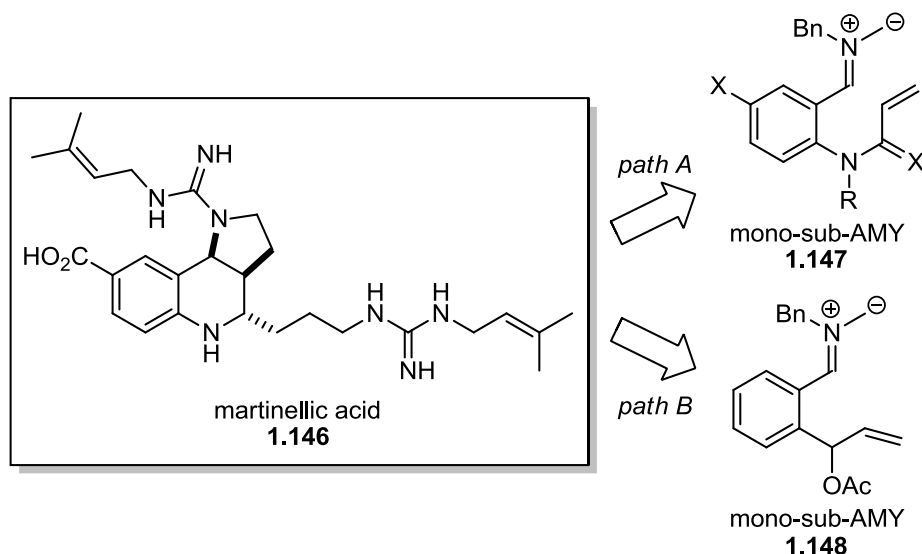


1.2.3.3 Martinellic Acid

The *Martinella* alkaloids, isolated from the South American plant *Martinella iquitosensis*, are non-peptidic antagonists for the bradykinin B1 and B2 receptors, which make these compounds interesting as potential anti-hypertensive agents.¹⁹ Furthermore, the novel tetrahydroquinoline structure has inspired a number of synthetic investigations into the synthesis of this class of molecules. Martinellic acid (**1.146**) is a classic representative of this alkaloid family and has been the target of numerous approaches to employ a 1,3-DPC to construct the natural product core. Two discrete approaches exploiting this disconnect can be defined that both construct the pyrrolidine ring via similar mono-substituted azomethine ylides (Scheme 1.22). Path A targets an azomethine ylide of type **1.147**, which would access the martinellic acid core directly, and has been explored by both the Snider and Lovely groups.²⁰⁻²² Path B, investigated by the Miyata group, targeted azomethine ylide **1.148** for use in a 1,3-DPC to construct a

carbocyclic ring system, which was expanded to the tetrahydroquinoline core via a nitrene-type ring expansion reaction.²³

Scheme 1.22. Retrosynthesis of Martinellic Acid



The first synthesis of martinellic acid using the 1,3-DPC approach came out of the Snider research group, which began with aniline **1.149**^x and Meldrum's acid-activated cyclopropane **1.150**^{xi} (Scheme 1.23). Heating both components in toluene gave rise to the corresponding pyrrolidinone which was oxidized with MnO₂ to give aldehyde **1.151** in 54% yield over two steps. A decarboxylative cycloaddition was thus carried out with N-benzylglycine in refluxing toluene to effect an intramolecular 1,3-DPC via ylide **1.152** to give the tricyclic martinellic acid core **1.153** in 60% yield in high diastereoselectivity. The tetracyclic cycloadduct was then converted in martinellic acid in an additional 10 synthetic steps, corresponding to a 15 step total synthesis of **1.146** in 2% overall yield.

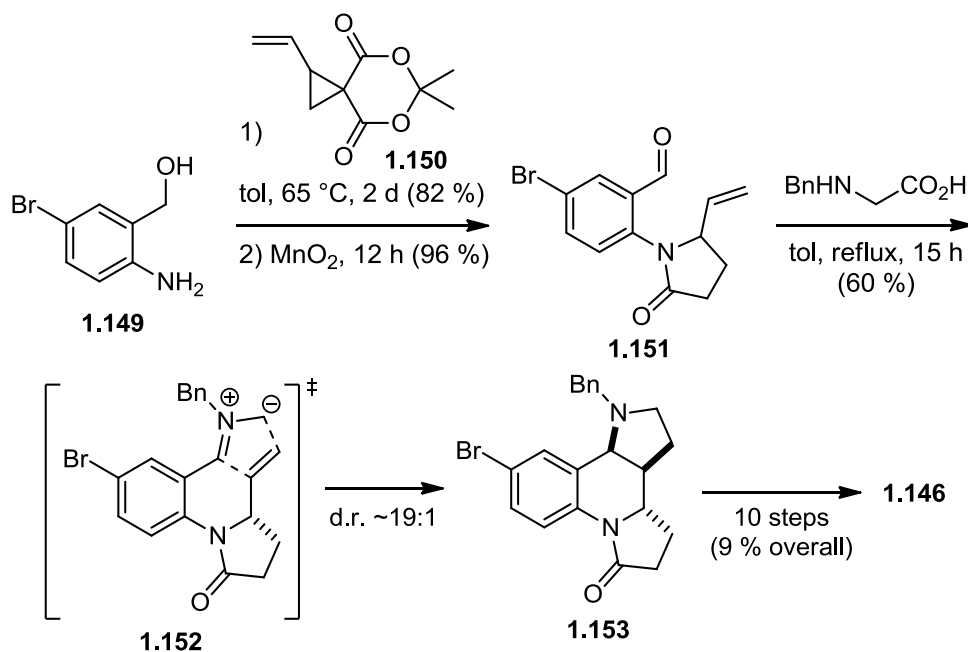
^x Synthesized in one step from methyl 4-bromoanthranilate in 81% yield.

^{xi} Synthesized in one step from 2-vinyl-1,1-cyclopropanedicarboxylic acid and isopropenyl acetate in 60% yield.

This total synthesis served as a crucial benchmark for this type of general strategy toward martinellie acid, not only with respect to the cycloaddition itself, but also established a useful endgame for the total synthesis.

Scheme 1.23. Snider – 1,3-DPC via Iminium Decarboxylation in Martinellie Acid

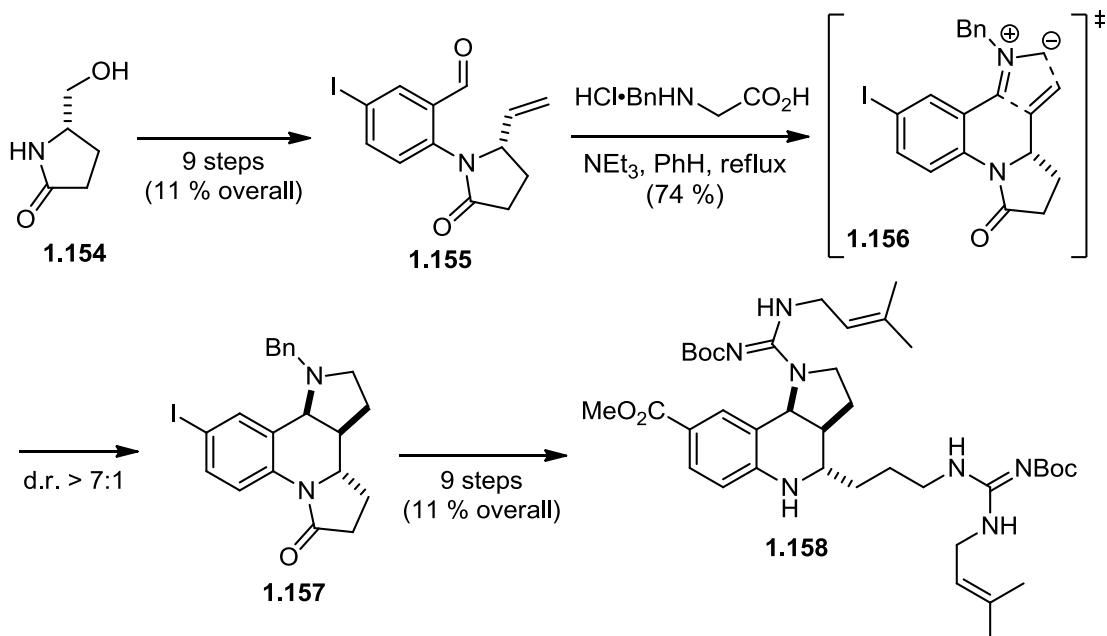
Total Synthesis



The Lovely group ultimately adopted the aforementioned Snider strategy in their own work while focusing on an asymmetric approach to martinellie acid (Scheme 1.24). Setting up an almost identical cycloaddition reaction with enantiopure aldehyde **1.155**, which was derived from pyrrolidinone **1.154** over a 9 step (11% overall) sequence. Refluxing aldehyde **1.155** with N-benzylglycine in benzene resulted in a decarboxylative azomethine ylide formation followed by an 1,3-DPC via **1.156** to give pyrrolidine **1.157** in 74% yield with good diastereoselectivity. An additional 9 steps were thus required to convert cycloadduct **1.157** into intermediate **1.158** following the general endgame

strategy Snider previously established. This effort constitutes a formal total synthesis of enantioenriched martinellie acid in 19 total steps and in ~1% overall yield.

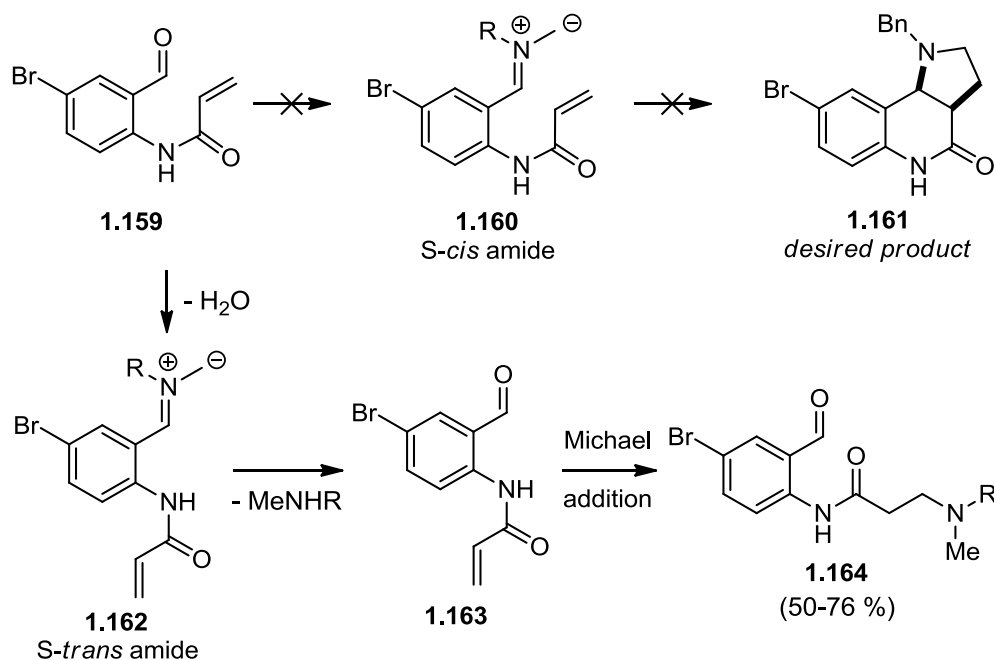
Scheme 1.24. Lovely – 1,3-DPC via Iminium Decarboxylation in Martinellie Acid
Formal Synthesis



Another cycloaddition strategy from the Lovely research group was subsequently reported wherein the core of martinellie acid was targeted using an intramolecular 1,3-DPC of ylide **1.160** (Scheme 1.25). This strategy would allow for a more accessible starting material to be applied to the cycloaddition. In their first attempt, the use of aldehyde **1.159** was probed, and interestingly no cycloaddition reaction was observed; rather the formation of amide **1.164** was the operable reaction pathway. Presumably this reaction did not work because the less favorable *S-cis* conformation of the amide was required for the cyclization. The more favorable *S-trans* conformer, on the other hand, cannot cyclize and thus hydrolyses, by virtue of the reversible nature of the reaction,

liberating N-benzyl-N-methylamine. This amine then reacts with the eneamide via an aza-Michael reaction to give amide **1.164** as the only identifiable product.

Scheme 1.25. Lovely – Failed Attempt at 1,3-DPC in Martinellie Acid Synthesis



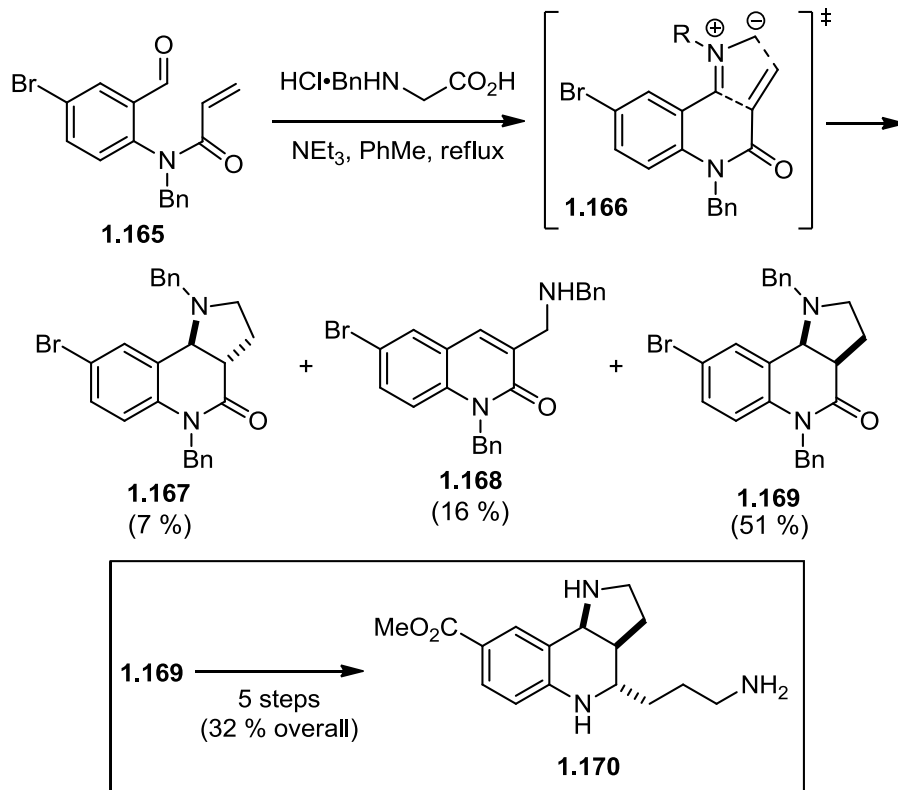
The *S-cis*/*S-trans* equilibrium of secondary amides is well-known to hinder cyclization reactions, and as such the use of an extra substituent on the amide nitrogen can be used to lower the barrier of rotation between the two conformers. To that end, amide **1.165**^{xii} was synthesized bearing a fully substituted amide nitrogen, and the cycloaddition reaction was tested again (Scheme 1.26). This time, heating the aldehyde with N-benzylglycine in refluxing toluene resulted in a facile cycloaddition reaction to give a mixture of three products. The desired cycloadduct **1.169** was formed in 51% yield, along with 7% of the undesired epimer **1.167**. The elimination product **1.168** was also formed in 16% under the reaction conditions. With cycloadduct **1.169** in hand, this

^{xii} Synthesized in three steps from methyl 4-bromoanthranilate in an undisclosed overall yield.

intermediate was advanced to amino compound **1.170** in five additional steps to complete a formal total synthesis of martinellie acid in eight total steps.

Scheme 1.26. Lovely – 1,3-DPC via Iminium Decarboxylation in Martinellie Acid

Formal Synthesis

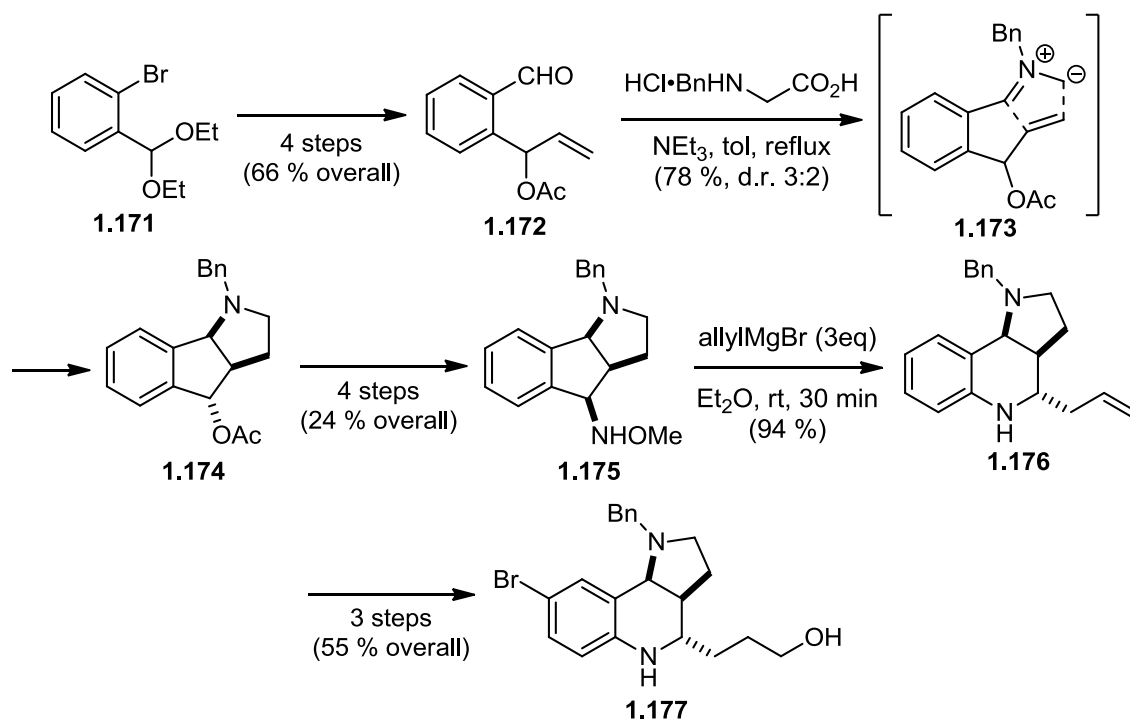


The final cycloaddition approach to martinellie acid comes out of the Miyata group, which aimed to employ a cascade ring-expansion/Mannich reaction that was previously been developed in their own group (Scheme 1.27). To set up this cascade reaction, the aldehyde **1.172** was prepared in four steps from acetal **1.171** in 66% overall yield. Refluxing the aldehyde with N-benzylglycine in refluxing toluene resulted in an intramolecular 1,3-DPC to give cycloadduct **1.174** in 78% yield as a mixture (3:2) of diastereomers. In four additional steps, **1.174** was converted to hydroxylamine **1.175**, at

which point their key cascade reaction could be employed to access the martinellie acid core. In the event, treatment of **1.175** with excess allyl Grignard resulted in a facile ring expansion to give the corresponding dihydroquinoline, which was subsequently alkylated with an additional equivalent of Grignard reaction via a Mannich-type reaction to give **1.176** in 94% yield. This molecule was then converted to aryl bromide **1.177** in three additional steps to give an intermediate which Snider used in his total synthesis of martinellie acid (refer to Scheme 1.23).

Scheme 1.27. Miyata – 1,3-DPC via Iminium Decarboxylation in Martinellie Acid

Formal Synthesis

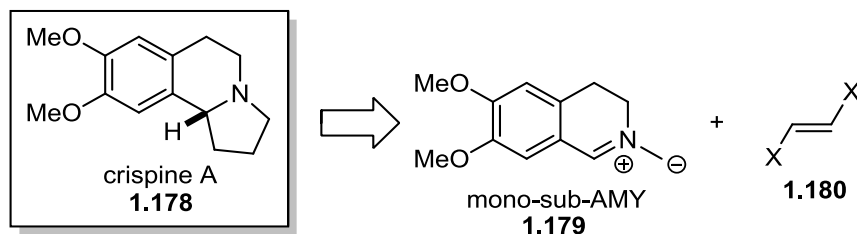


1.2.3.4 Crispine A

Crispine A (**1.178**) is a fairly simple alkaloid isolated from the *Carduus crispus* plant. The extracts from this plant have been used in Chinese folk medicine to treat

symptoms of cold, stomach ache, and rheumatism. Moreover, the extracts have been shown to possess *in vitro* anticancer and cytotoxic activity. While there have been quite a few syntheses of crispine A since its isolation, the Coldham synthesis serves as an example of a very efficient construction of this molecule using a novel 1,3-DPC cascade reaction, which has been investigated extensively in his group.^{24, 25} The pyrrolidine ring of crispine A (**1.178**) was envision coming from an intermolecular 1,3-DPC reaction of ylide **1.179** and an activate dipolarophile of type **1.180** (Scheme 1.28). On the surface, this strategy seems quite straightforward; however, the formation of the azomethine ylide was accomplished using a very novel intramolecular imine alkylation/iminium decarboxylation cascade.

Scheme 1.28. Retrosynthesis of Crispine A



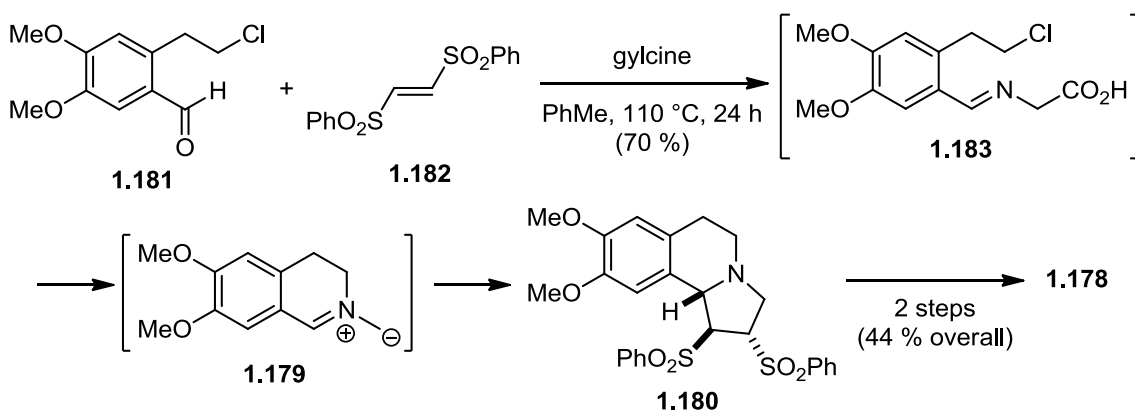
The Coldham synthesis of the crispine A core was accomplished by heating chloroaldehyde **1.181**^{xiii} with bisphenylvinylsufone **1.182** and glycine in refluxing toluene (Scheme 1.29). After condensation of the aldehyde moiety with glycine, an intramolecular imine alkylation of **1.183** delivered the requisite iminium ion, which spontaneously decarboxylated to give azomethine ylide **1.179**. This azomethine ylide then underwent intermolecular 1,3-DPC to give the crispine A core **1.180** in 70% yield as an undisclosed mixture of diastereomers favoring that shown. The efficiency of this

^{xiii} Synthesized in two steps from 3,4-dimethoxyphenethyl alcohol in 32% overall yield.

cascade reaction is quite remarkable in that the tricyclic core of crispine A was constructed in one operation from mostly acyclic starting materials. With **1.180** in hand, two additional steps were required to desulfurize the pyrrolidine ring and deliver crispine A in a synthetic sequence requiring 5 total steps and in 10% overall yield.

Scheme 1.29. 1,3-DPC via Imine Alkylation/Decarboxylation Cascade in Crispine A

Total Synthesis

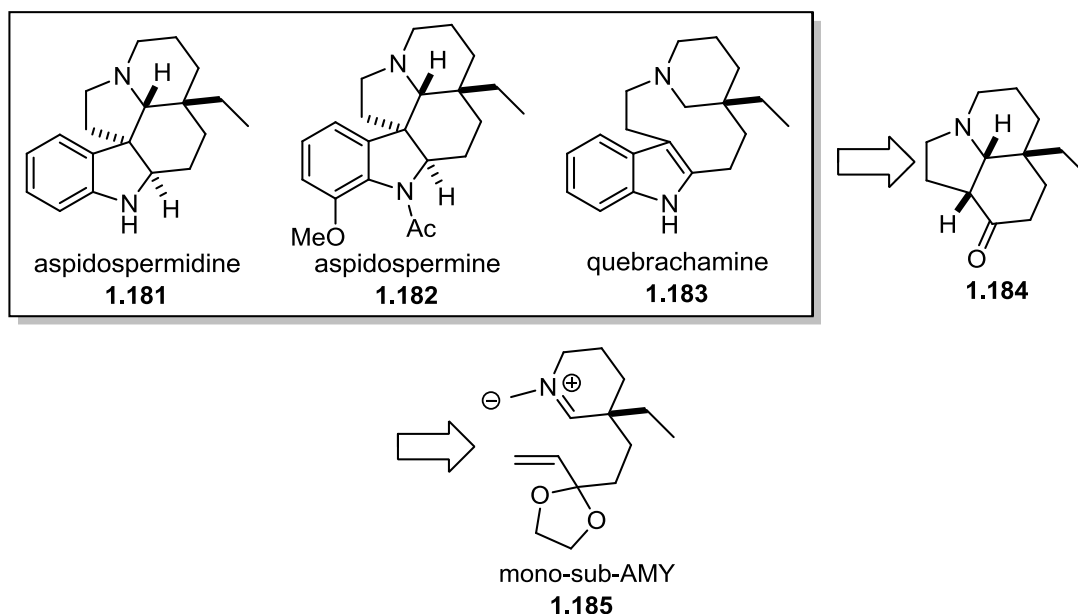


1.2.3.5 *Aspidosperma* Alkaloids

The synthesis of crispine A itself was not as remarkable as the efficiency of the cascade strategy that the Coldham group has developed. In an effort to further showcase this methodology, an impressive approach to the aspidosperma alkaloids was thus developed (*vide infra*).^{26, 27} The aspidosperma alkaloids are arguably some of the most well studied class of natural products, not only with respect to their synthetic studies dating back almost 50 years, but these alkaloids exhibit a wide range of interesting biological activity. A common intermediate, often targeted by synthetic groups, is ketone **1.184** (Scheme 29), which was first elaborated into aspidospermine (**1.182**) and quebrachamine (**1.183**) by Stork in 1963. Coldham similarly targeted this ketone;

however, he aimed to apply his imine alkylation/iminium decarboxylation cascade reaction to target ylide **1.185**.

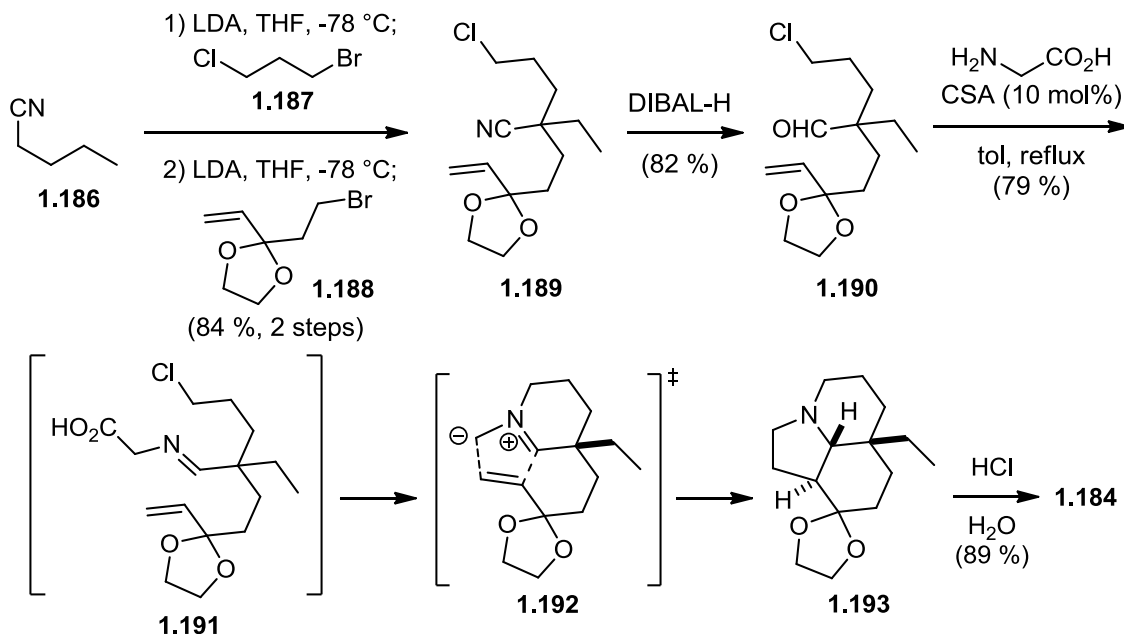
Scheme 1.30. Retrosynthesis of Aspidosperma Alkaloids



Coldham's approach to the aspidosperma alkaloids began with the expeditious assembly of aldehyde **1.190** via a two-step alkylative coupling of fragments **1.186**, **1.187**, and **1.188** followed by DIBAL reduction of the resulting cyano-compound **1.189** to give aldehyde **1.190** in 69% overall yield (Scheme 1.31). Aldehyde **1.190** was then heated with glycine and catalytic camphorsulfonic acid in refluxing toluene to give an intermediate imine, which underwent intramolecular alkylation and decarboxylation of the resulting iminium ion to give azomethine ylide **1.185**. This ylide then reacted with the tethered, unactivated olefin via the transition state **1.192** to give the aspidosperma core **1.193** in 79% yield. This cascade reaction very efficiently constructed the target tricyclic core in one operation from acyclic starting materials, which could subsequently

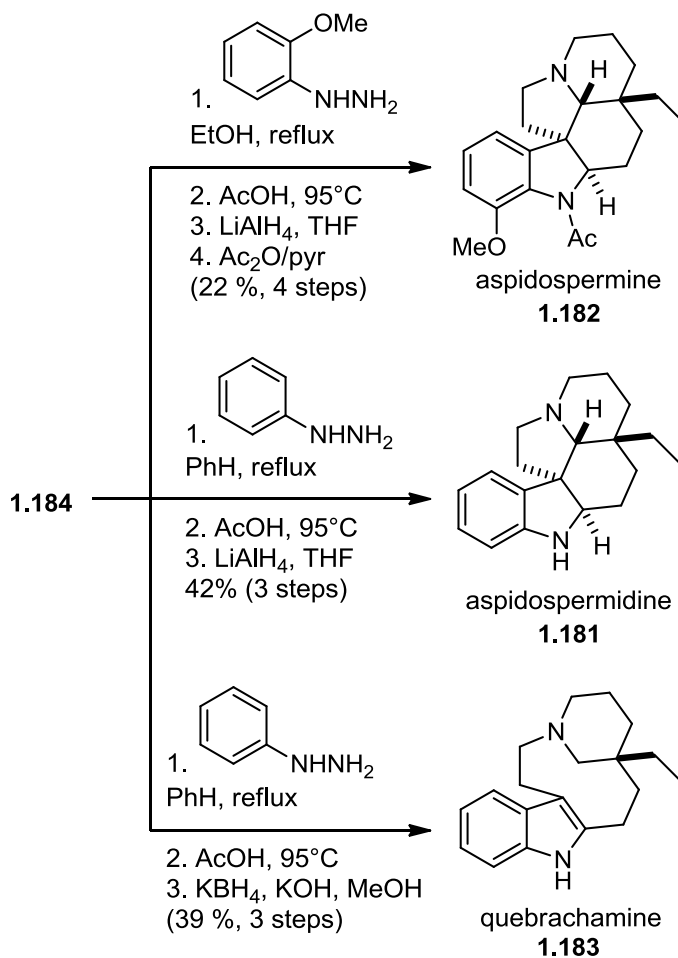
be hydrolyzed to give the Stork ketone **1.184** in 6 total synthetic steps and in an impressive 40% overall yield.

Scheme 1.31. 1,3-DPC via Imine Alkylation/Decarboxylation Cascade in Aspidosperma Alkaloid Synthesis



The intermediate Stork ketone **1.184** was then elaborated, using literature conditions, into aspidospermine (**1.182**), aspidospermidine (**1.181**), and quebrachamine (**1.183**) through three separate sequences involving a Fischer indole synthesis to install the indole moiety in each case (Scheme 1.32).

Scheme 1.32. Utilizing the 1,3-DPC Product as a Common Synthetic Intermediate in the Total Syntheses of Aspidosperma Alkaloids



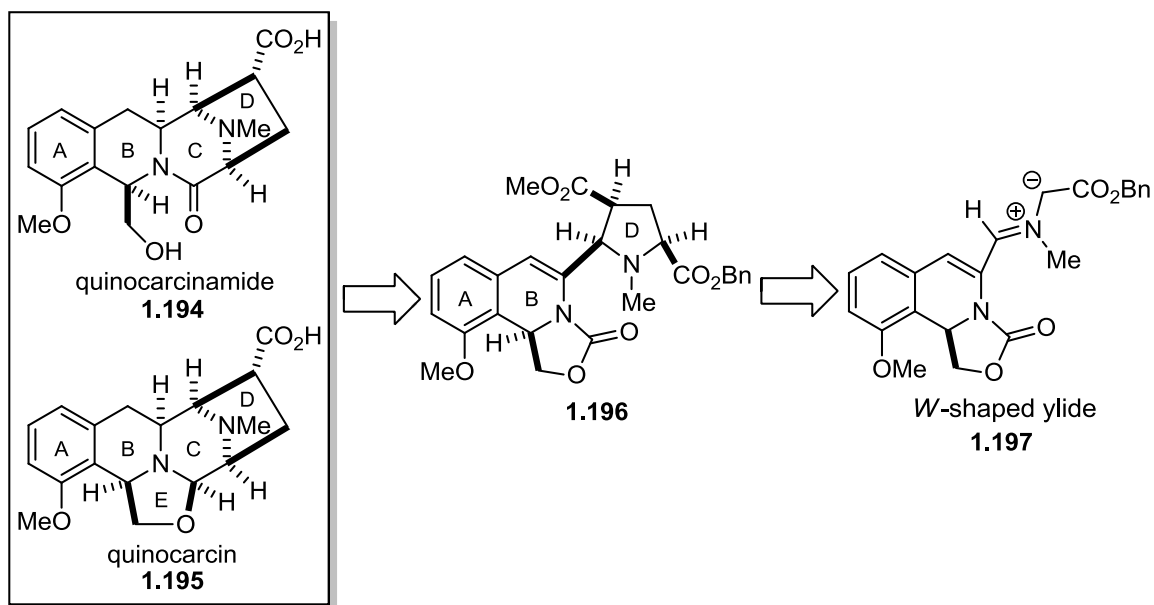
1.2.4 Applications Involving the Deprotonation of Iminium Ions

1.2.4.1 *Quinocarcin & Quinocarcinamide*

Quinocarcin (**1.195**) is a natural secondary metabolite isolated from *Streptomyces melanovinaceus*, which has been shown to exhibit antimicrobial activity against several Gram-positive microbes, and has also exhibited anti-tumor activity as its citrate salt. The naturally occurring oxidative byproduct quinocarcinamide (**1.194**), however, has shown

to be biologically inactive. These alkaloids have succumb to many syntheses, and, in particular, the work of Williams has illuminated a strategy toward the construction of the azabicyclic framework via a novel 1,3-DPC cycloaddition (Scheme 1.33, see also Sections 1.2.6.3, 1.2.5.1, and 1.2.7.2 for a related discussion of these alkaloids).²⁸⁻³¹ The original method used was aimed at creating the pyrrolidine ring system in **1.196** using the 1,3-disubstituted azomethine ylide **1.197** in an intermolecular 1,3-DPC with an acrylate dipolarophile. As described earlier in this review, most acyclic 1,3-disubstituted azomethine ylides tend to favor the *S*-shape, however, in this case they were hoping to access the *cis*-ylide of type **1.197** (*W*- or *U*-shaped).

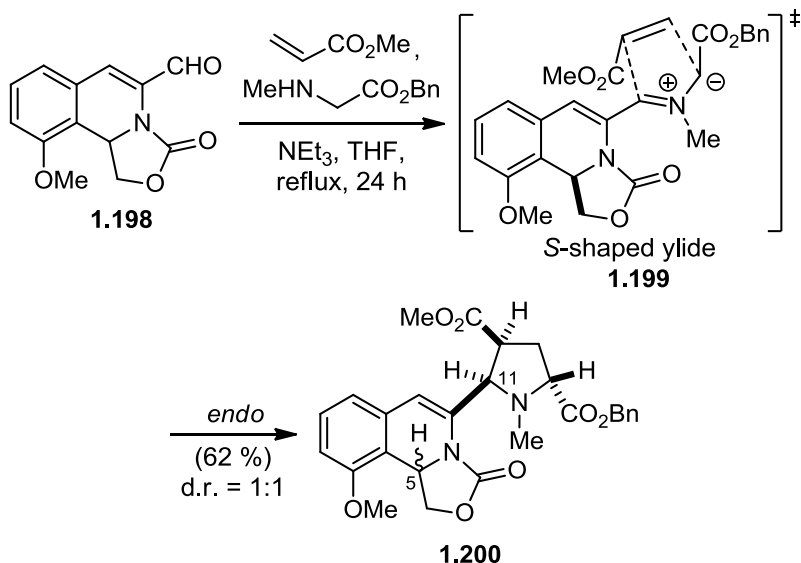
Scheme 1.33. Retrosynthesis of Quinocarcin & Quinocarcinamide



Their first attempt to execute the cycloaddition strategy started with aldehyde **1.198** (Scheme 1.34). Heating **1.198** with benzyl *N*-methylglycinate and triethylamine in refluxing THF furnished an azomethine ylide via iminium deprotonation, which reacted

with methyl acrylate to give pyrrolidine **1.200** via the *endo*-transition state **1.199**. It was hoped that the stereochemistry at C(5) would be sufficient in directing the facial selectivity of the cycloaddition event, however a mixture (1:1) of *syn*- and *anti*-diastereomers was obtained (relative to C(5) and C(11)). In assigning the stereochemistry of the pyrrolidine ring it was determined that the ring possessed a 2,5-*anti*-relationship, which would suggest the reaction proceeded through an *S*-shaped azomethine ylide **1.199** and not the desired *cis*-ylide. With the incorrect stereochemistry from the cycloaddition to continue forward with the total synthesis, a revised route was drafted to address the azomethine ylide geometry.

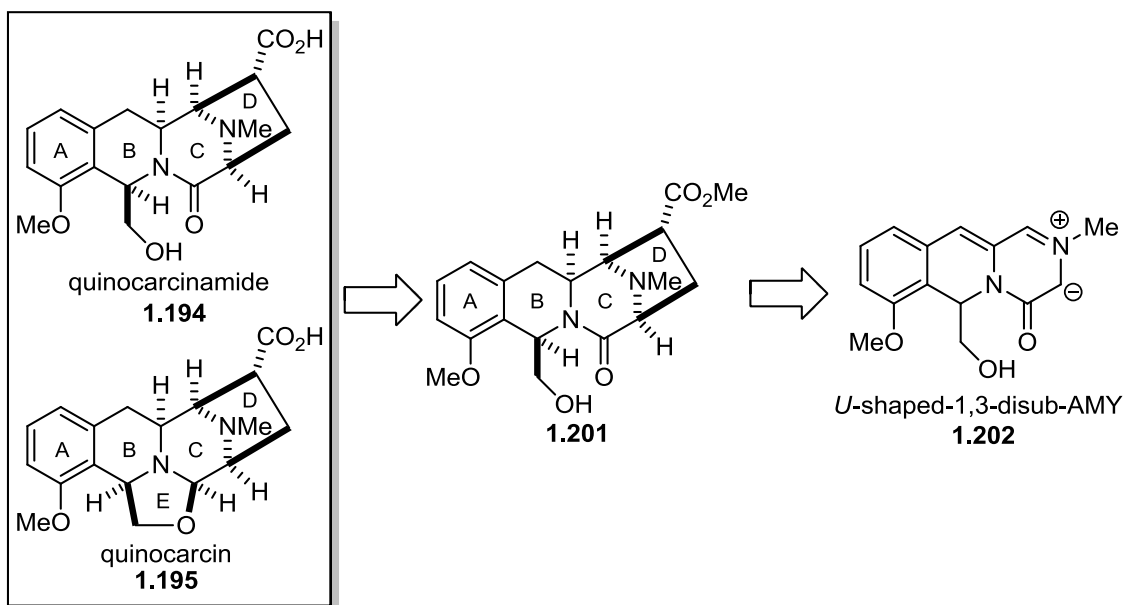
Scheme 1.34. Initial Attempt at 1,3-DPC via Iminium Deprotonation to Form Quinocarcinamide Core



In the revised approach, Williams next aimed to employ the cyclic azomethine ylide **1.202**, which would, by virtue of the cyclic nature of the reactive species, give the

desired *U*-ylide geometry (Scheme 1.35). This cycloaddition would give direct access to the quinocarcin core **1.201**.

Scheme 1.35. Revised Retrosynthesis of Quinocarcin & Quinocarcinamide



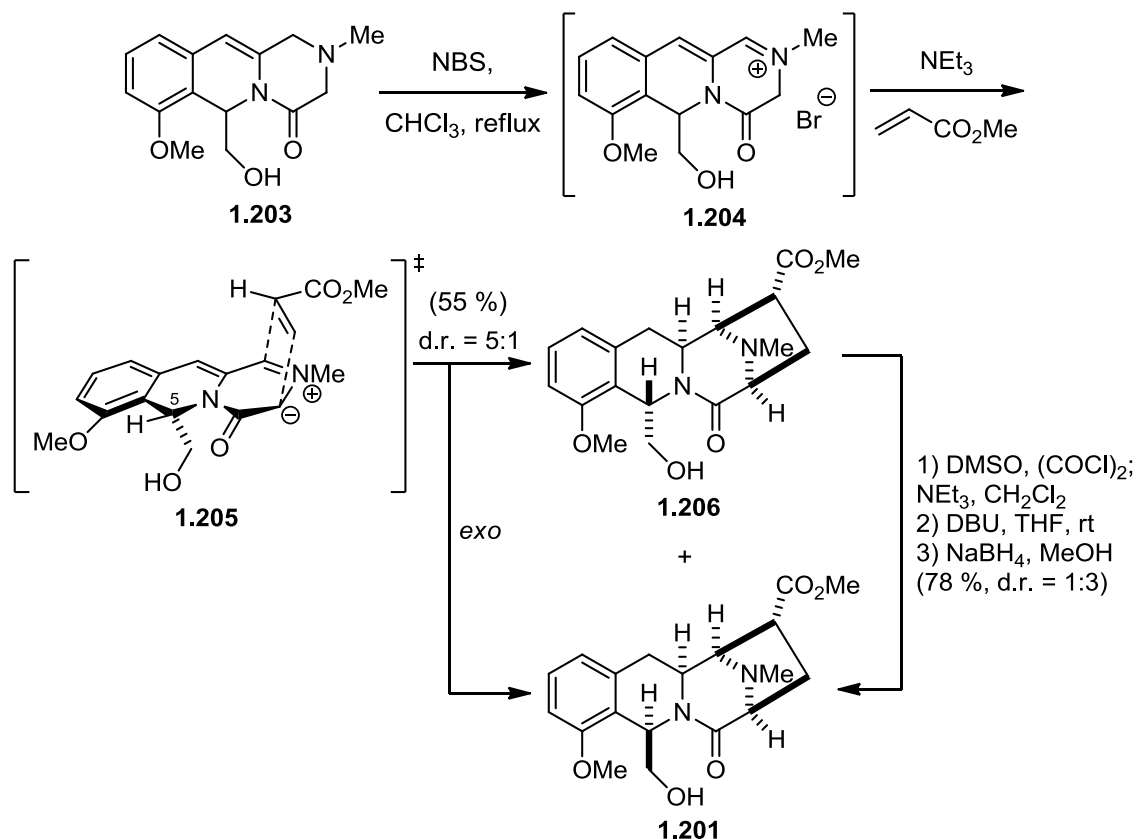
The second approach to the cycloaddition used piperazine derivative **1.203**^{xiv}, which was first activated as a highly conjugated iminium salt **1.204** by treatment with NBS (Scheme 1.36). This salt was an isolable green solid that, when treated with base, formed a cyclic azomethine ylide and reacted in an intermolecular 1,3-DPC via transition state **1.205** to give a 55% yield of a mixture (1:5) of diastereomers favoring **1.206**. In both of the diastereomers, the cycloaddition was *exo*-selective to give the desired stereochemistry of the azabicyclic moiety. The major product, however, had the incorrect stereochemistry at C(5) due to approach of the dipolarophile from the face opposite the methanol side chain. Fortunately, the C(5) stereocenter could be

^{xiv} Synthesized in 16 steps from *o*-anisaldehyde in 8% overall yield.

equilibrated to the desired relative stereochemistry via oxidation and thermodynamic equilibration of the corresponding aldehyde. In this way, the major product of the cycloaddition could be efficiently converted to the desired product **1.201**.

Scheme 1.36. 1,3-DPC via Iminium Deprotonation in the Quinocarcinamide Total

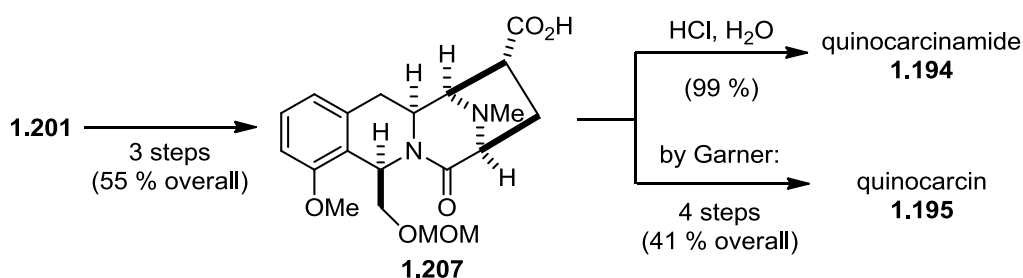
Synthesis



With the quinocarcin core **1.201** in hand, the synthesis of quinocarcinamide (**1.195**) could be completed in 4 additional steps to complete the total synthesis in 25 total synthetic steps in 2% overall yield (Scheme 1.37). The intermediate **1.207** *en route* to quinocarcinamide was previously carried forward to quinocarcin by Garner, which would also constitute a Williams formal total synthesis of quinocarcin.³² It is important to note,

that this synthetic effort further highlights the preference for acyclic 1,3-disubstituted azomethine ylides to favor the *S*-shaped geometry. In order to access *cis*-ylides of this type, extra measure and consideration must be taken. In the case of the quinocarcinamide total synthesis, the strategy that worked best was tying the ylide in a cyclic conformation.

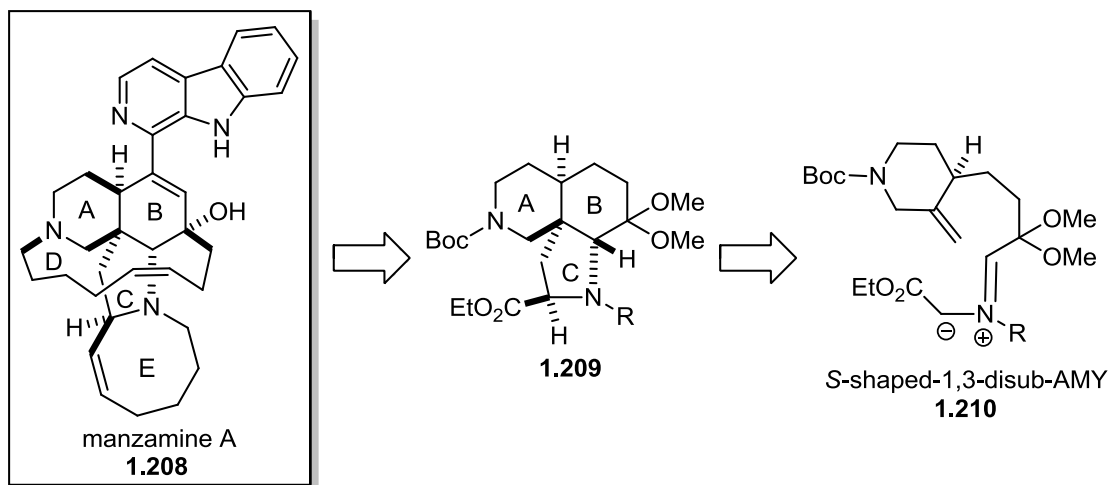
Scheme 1.37. Completion of Quinocarcinamide (1.194) Synthesis and Quinocarcin (1.195) Formal Synthesis



1.2.4.2 Manzamine A

Manzamine A (**1.208**) was isolated from the blue Caribbean marine sponge *Haliclona caerulea*, and has been shown to exhibit potent antitumor and antimalarial activity. While this incredibly unique architectural framework has garnered much attention from the synthetic community on a few total syntheses have been completed. A majority of the synthetic efforts which have been reported focus on the construction of the ABC and ABCE core of the molecule. One such report by Coldham targeted the C-ring using an intramolecular 1,3-DPC reaction via an *S*-shaped-1,3-disubstituted azomethine ylide **1.210** (Scheme 1.38).³³ This reaction would give the ABC ring system **1.209** directly, which would contain the requisite stereochemistry and functionality to construct the E ring.

Scheme 1.38. Retrosynthesis of Manzamine A



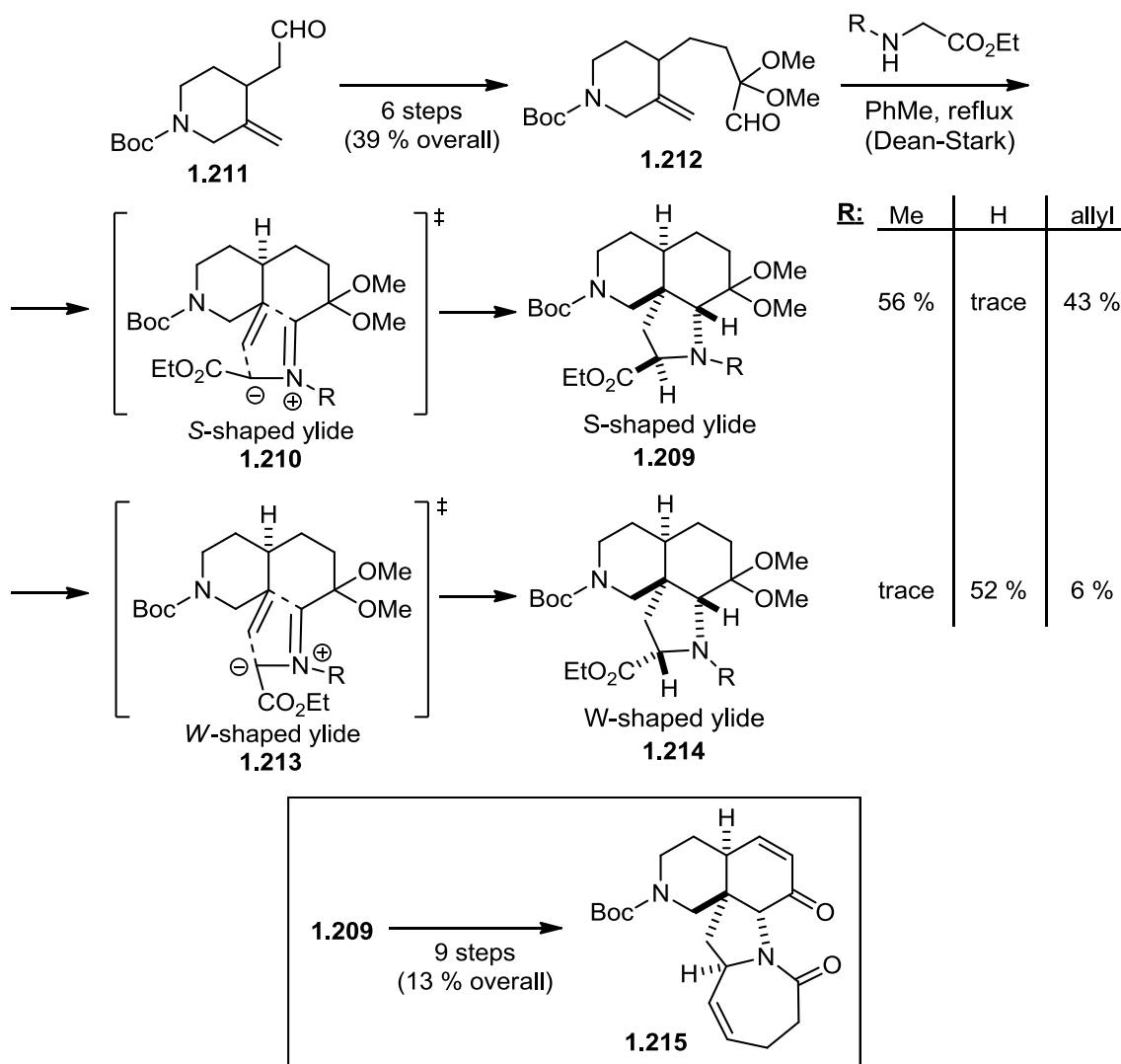
The synthesis began with aldehyde **1.211**^{xv}, which was elaborated into aldehyde **1.212** in 6 steps and 39% overall yield (Scheme 1.39). This aldehyde was then heated with a variety of glycinate esters in refluxing toluene to give a mixture of azomethine ylides **1.210** and **1.213** bearing the *S*- and *W*-geometry, respectively. The *S*-ylide was generally favored and thus gave the desired cycloadduct **1.209**, bearing the 2,5-*trans*-pyrrolidine moiety. Since the N-methyl example was not synthetically viable, the use of ethyl N-allylglycinate was used for subsequent progress in the total synthesis. It is also noteworthy, that the non-substituted nitrogen example (using glycine ethyl ester) led to a complete inversion of the stereoselectivity giving primarily pyrrolidine **1.214**. As was discussed earlier in this review, acyclic azomethine ylides tend to inherently favor the *S*-geometry, due to minimization of *pseudo*-A_{1,3} strain between the group on the nitrogen and the group at the 1-position of the ylide. As is sometimes the case with protonated ylides (exemplified in Scheme 1.39), adopting the *W*-geometry can be the more favorable option. With pyrrolidine **1.209** in hand, Coldham further elaborated the manzamine core

^{xv} Synthesized in five steps from arecoline in 52% overall yield.

though a 9 steps series of refunctionalizations and construction of the E-ring using a ring closing metathesis strategy to deliver **1.215**. The overall synthesis of the tetracyclic manzamine core **1.215** was accomplished in 21 total synthetic steps and in 1% overall yield.

Scheme 1.39. 1,3-DPC by Iminium Deprotonation in Manzamine A Partial

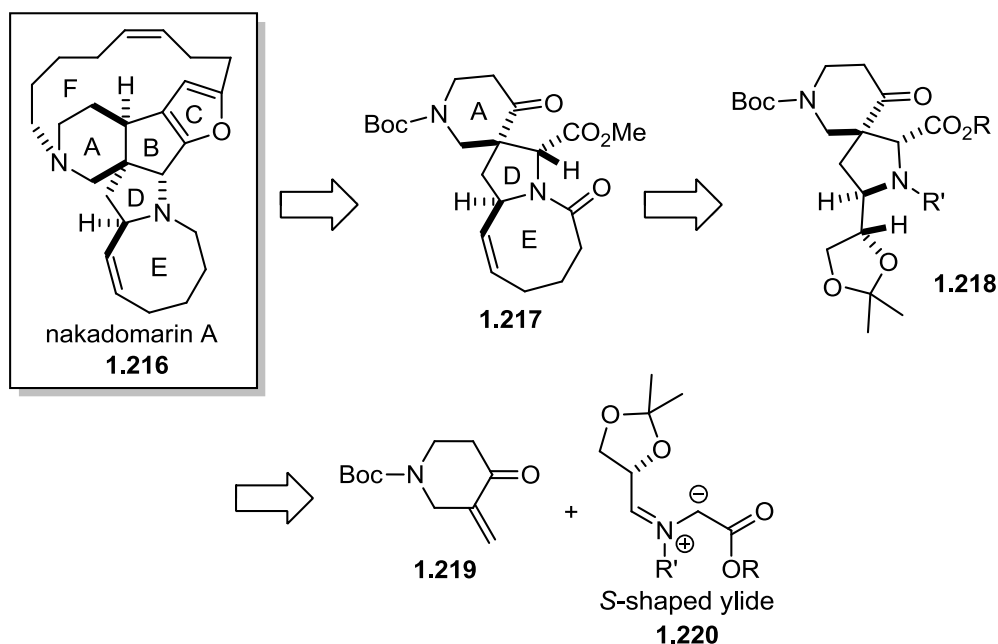
Synthesis



1.2.4.3 *Nakadomarin A*

Nakadomarin A (**1.216**), which was first isolated from the sponge *Amphimedon* *sp.* (SS-264), is a manzamine alkaloid thought to be a biogenetic precursor to manzamine A (**1.208**). Nakadomarin A exhibits an array of biological activities including cytotoxicity against murine lymphoma, inhibition of cyclin dependent kinase 4, antimicrobial, and antibacterial activity. Additionally, the furan C ring of nakadomarin A makes it unique in the manzamine family; the ADE rings, however, are closely related to the other manzamine alkaloids. In fact, similar to the manzamine synthesis described in the previous section, the pyrrolidine ring in **1.216** was targeted by Williams for construction using a novel asymmetric 1,3-DPC reaction (Scheme 1.40).^{34, 35} Targeting a chiral *S*-shaped azomethine ylide of type **1.220**, a 1,3-DPC was envisioned occurring with the activated exocyclic olefin **1.219** in an *endo*-fashion to give the 2,5-*anti*-pyrrolidine **1.218**. This could then be used to construct the remaining E-ring to deliver tricycle **1.217**.

Scheme 1.40. Retrosynthesis of Nakadomarin A



The Williams cycloaddition addresses two critical issues related to azomethine ylide 1,3-DPCs. First, the general formation of 1,3-disubstituted azomethine ylides bearing a discrete *S*-shape, and second, the induction of asymmetry using a chiral azomethine ylide. For the most part, the asymmetric examples of 1,3-DPC mostly rely on chiral dipolarophiles as a source of asymmetric induction. The Williams group, on the other hand, has developed a class of chiral azomethine ylides based on condensation of amine **1.56**^{xvi} with a desired aldehyde (Scheme 1.41). The azomethine ylides that form from this process always bear an *S*-shaped azomethine ylide, a consequence of the side chain from the aldehyde taking up the least hindered hemisphere to avoid a steric interaction with the benzyl amine stereocenter. This method of generating azomethine ylides has been very thoroughly explored by the Williams group and has been developed

^{xvi} Synthesized in one step from the commercially available N-Boc analogue.

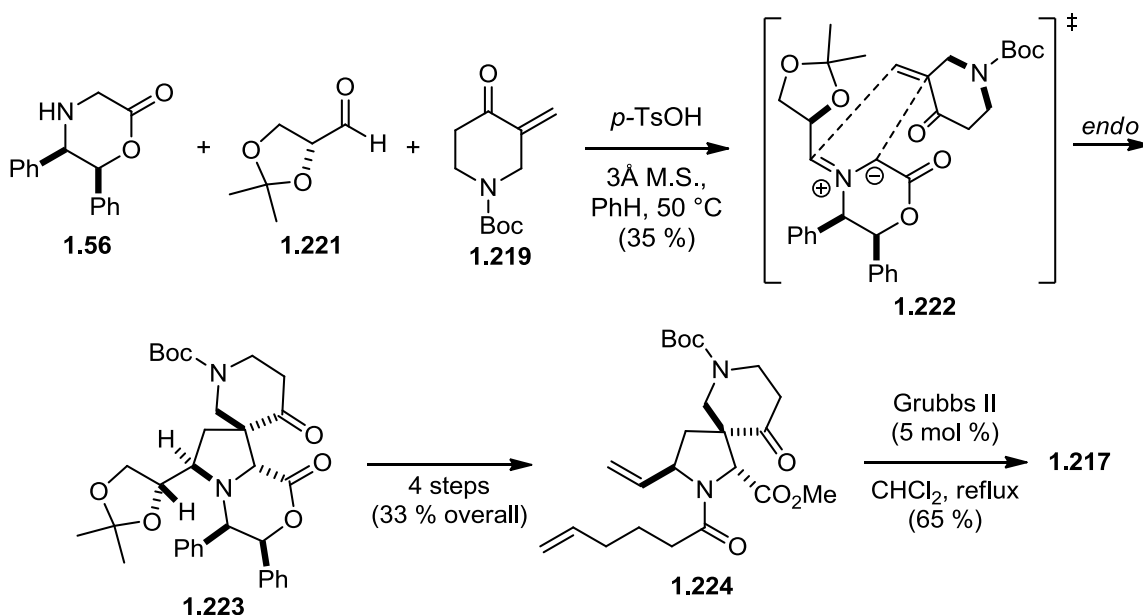
into a general method for the construction of 2,5-*trans*-pyrrolidines. In the case of nakadomarin A, the multicomponent 1,3-DPC cycloaddition with **1.221**, **1.219**^{xvii}, and **1.56**^{xviii} was performed by heating the three components with *p*-TsOH in benzene, which resulted in an *S*-shaped-1,3-disubstituted azomethine ylide. This ylide underwent intermolecular 1,3-DPC with **1.219** via the *endo*-transition state **1.222** to give pyrrolidine **1.223** in 35% yield, which constitutes construction of the A and D rings of nakadomarin A. It is important to note, that enolizable aldehydes are notoriously difficult to employ in this type of azomethine ylide formation reaction, which may explain the lower yield of the cycloaddition. Considering, however, that the cycloaddition reaction delivered the complex and enantiopure **1.223** in a single operation, this cycloaddition reaction was still highly effective. An additional 4 steps set up an olefin metathesis of **1.224** to construct the E ring and give **1.217** in 10 total synthetic steps and in <4% overall yield.

^{xvii} Synthesized in two steps from N-Boc-piperidone in ~50% yield. Note: enone is unstable and was used immediately following preparation.

^{xviii} Synthesized in one step from 1,2,5,6-di-O-isopropylidene-D-mannitol.

Scheme 1.41. Asymmetric 1,3-DPC via Iminium Deprotonation in Nakadomarin A

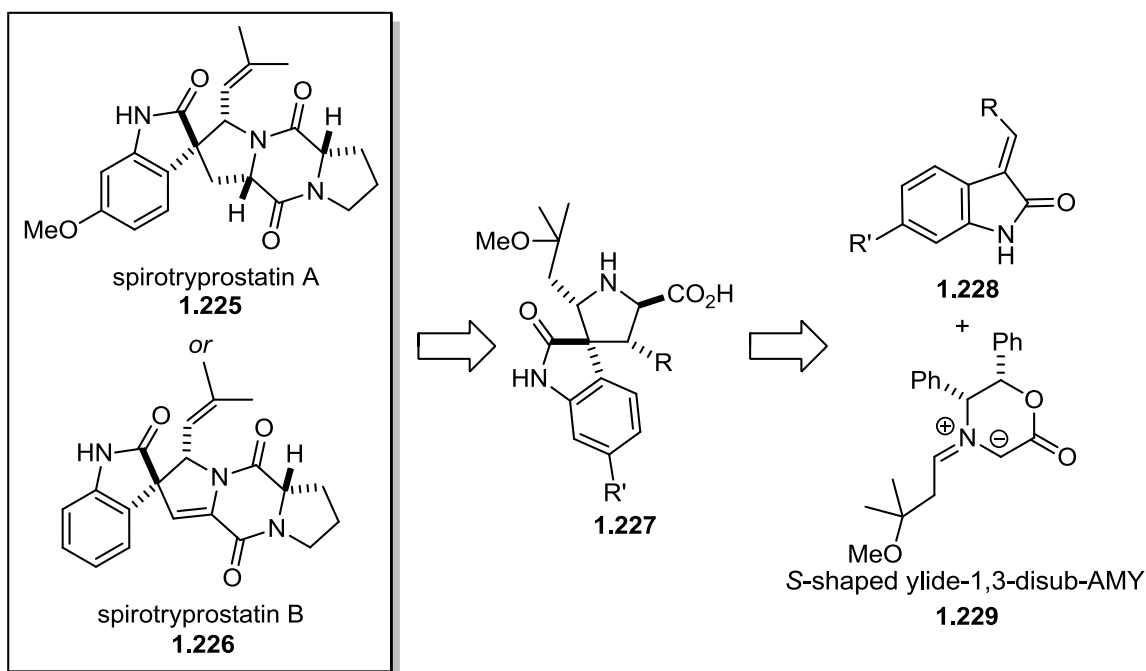
Partial Synthesis



1.2.4.4 Spirotryprostatin A & B

The spirotryprostatins were isolated from *Aspergillus fumigatus* are part of the larger class of tryprostatin alkaloids, which have potential as antimitotic arrest agents. The spirotryprostatins in particular, have shown moderate cell progression inhibition. The Williams group targeted spirotryprostatin A (**1.225**) and B (**1.226**) using an asymmetric intermolecular 1,3-DPC with a chiral azomethine ylide possessing the *S*-geometry (**1.229**), which would give access to the proline derivative **1.227** (Scheme 1.42).³⁶⁻³⁸ In order to accomplish the asymmetric 1,3-DPC, the Williams group aimed to further explore the chiral azomethine ylide technology that they previously developed and applied to the partial synthesis of nakadomarin A (See previous section, 1.2.4.3).

Scheme 1.42. Retrosynthesis of Spirotryprostatin A

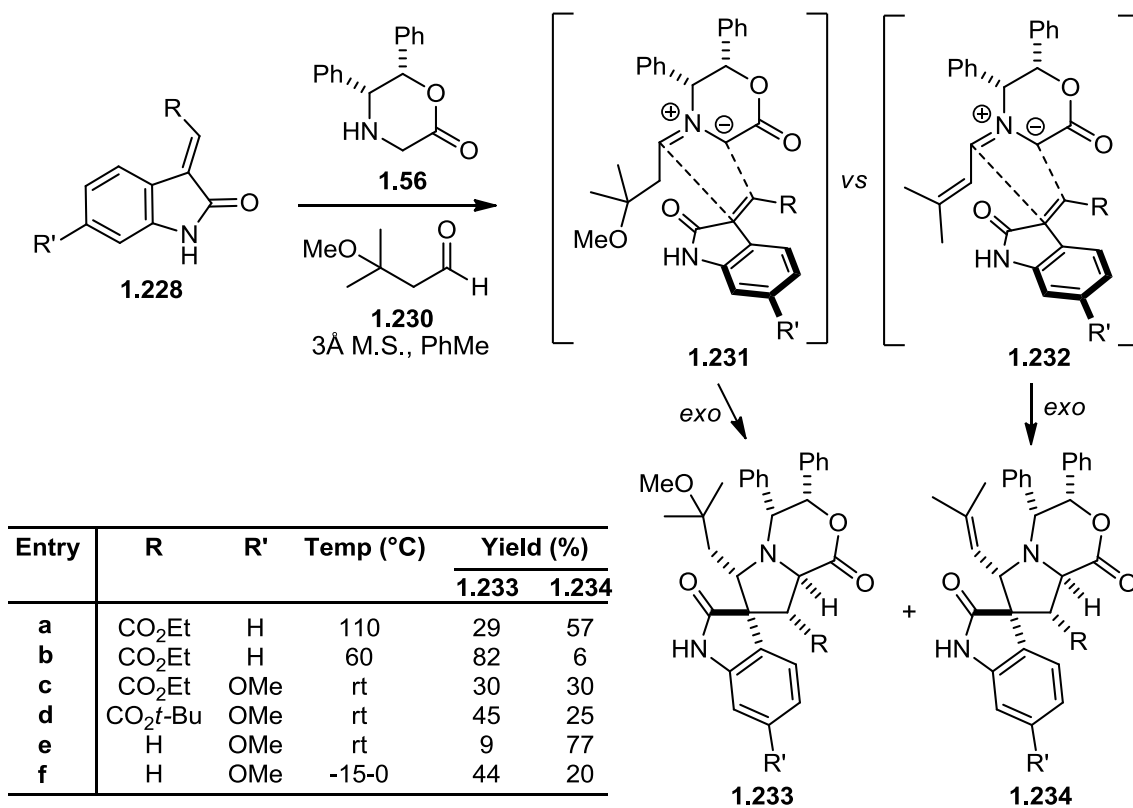


The asymmetric cycloaddition reaction was assayed to discover an optimal dipolarophile and set of conditions for constructing the partial spirotryprostatin core **1.232** (Scheme 1.43). Along with chiral amine **1.56** and aldehyde **1.230**, a series of oxindole derivatives **1.228a-f**^{xix} were screened, and upon mixing in toluene, the mixture surprisingly gave two different azomethine ylides. Both ylides underwent cycloaddition via their respective intermolecular *exo*-transition states **1.231** and **1.232** to yield the corresponding pyrrolidines **1.233** and **1.234**, respectively. Surprisingly, no observable *endo*-products formed during the course of the reaction; however, a significant steric clash with the vicinal phenyl groups on the chiral auxiliary and the R-group of the dipolarophile can be envisioned encumbering the *endo*-transition states. Also not

^{xix} Oxindole **1.228a** was synthesized in one step from isatin in 84% yield. Oxindole **1.228e** was synthesized in two steps from 6-methoxyisatin in ~80% and was found to be unstable.

expected, was the formation of the olefin products such as **1.234**. The possibility of these forming after the cycloaddition event, by elimination of **1.233**, was ruled out by resubjecting the ether products to the cycloaddition conditions and only starting materials were recovered. It was thus postulated that the eliminated cycloadducts **1.234** were formed from a discrete azomethine ylide species **1.232**, which suggests that the elimination occurred during or prior to the ylide formation.

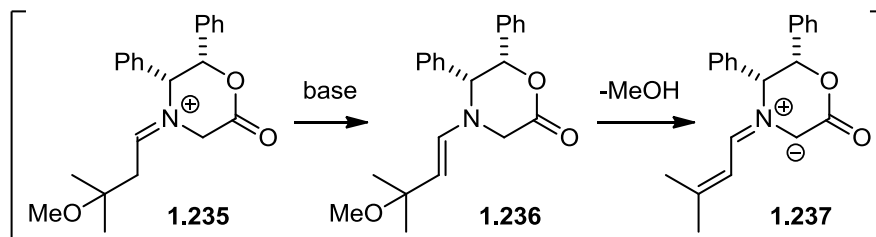
Scheme 1.43. 1,3-DPC via Iminium Deprotonation in Spirotryprostatin A/B Total Syntheses



The formation of ylides **1.232** in the above cycloaddition examples, serve to illuminate the challenge of using enolizable aldehydes in ylide formation reactions. From

a mechanistic perspective, the conjugated ylides **1.232** were presumably formed by tautomerization of the iminium species **1.235** to give enamine **1.236** (Scheme 1.44). Since the enamine is essentially a vinylogous N,O-acetal, the elimination of a molecule of MeOH is very facile, and results in ylide **1.237**. In cycloaddition reactions where enolizable aldehydes are used, and there is no β -leaving group, the formation of enamines by this mechanism is what presents the biggest hurdle to successfully performing 1,3-DPC of this type.

Scheme 1.44. Elimination Mechanism for the Formation of Ylide 1.237

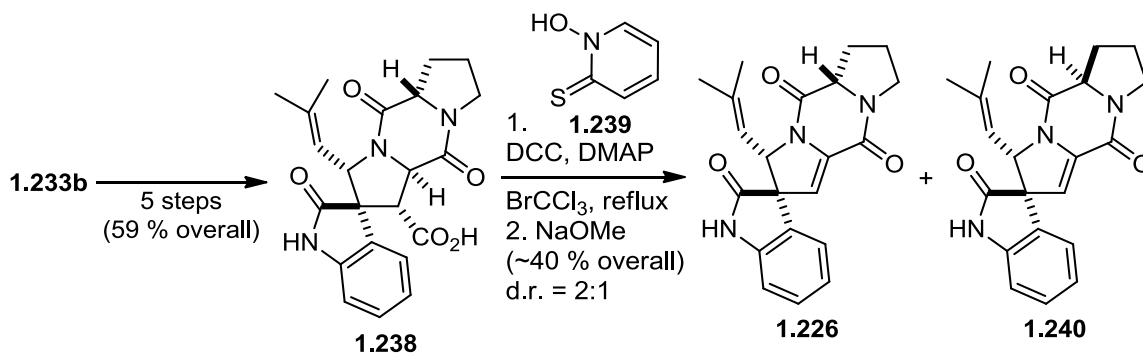


A majority of the effort that went in to optimizing the cycloaddition reactions for the spirotryprostatins was focused simply on avoiding the elimination problem. The eliminated products, despite mapping on to the natural products, were not found to be compatible with the conditions for removal of the chiral auxiliary; therefore conditions that gave **1.233** preferentially were required for progress going forward. With respect to spirotryprostatin B (Scheme 1.43, entries a and b, $R'=H$), it was discovered that lower reaction temperatures and longer reaction times were crucial to avoid the eliminated cycloadducts. With respect to spirotryprostatin A (Scheme 1.43, entries c-f, $R'=OMe$), a number of different systems were investigated to avoid the eliminated product. The *t*-butyl ester (entry d) gave the best result for the carboxylated entries, however, subsequent steps in the synthesis revealed that the Hunsdiecker reaction that was envisioned for

removal the carboxylic acid failed to provide the desired product. It was necessary to therefore perform the cycloaddition to give the hydro-derivatives directly (Scheme 1.43, entries e & f). Initially, as exemplified by entry e, these cycloaddition reactions gave mostly the undesired elimination product. It was eventually found that low temperatures (<0 °C) and longer reaction times were crucial to obtain any synthetically useful amount of the desired product **1.233**.

The synthesis of spirotryprostatin B was completed using the cycloadduct **1.233b**, which could be converted to carboxylic acid **1.238** in an additional five steps and 59% overall yield following the cycloaddition (Scheme 1.45). Next, a Barton-modified Hunsdiecker was used to install a bromide, which was subsequently eliminated to give a mixture (2:1) of spirotryprostatin B (**1.226**) and 12-*epi*-spirotryprostatin B (**1.240**) in 40% yield over the two step sequence. The total synthesis of **1.226** was thus accomplished in 10 total synthetic steps and in 10% overall yield.

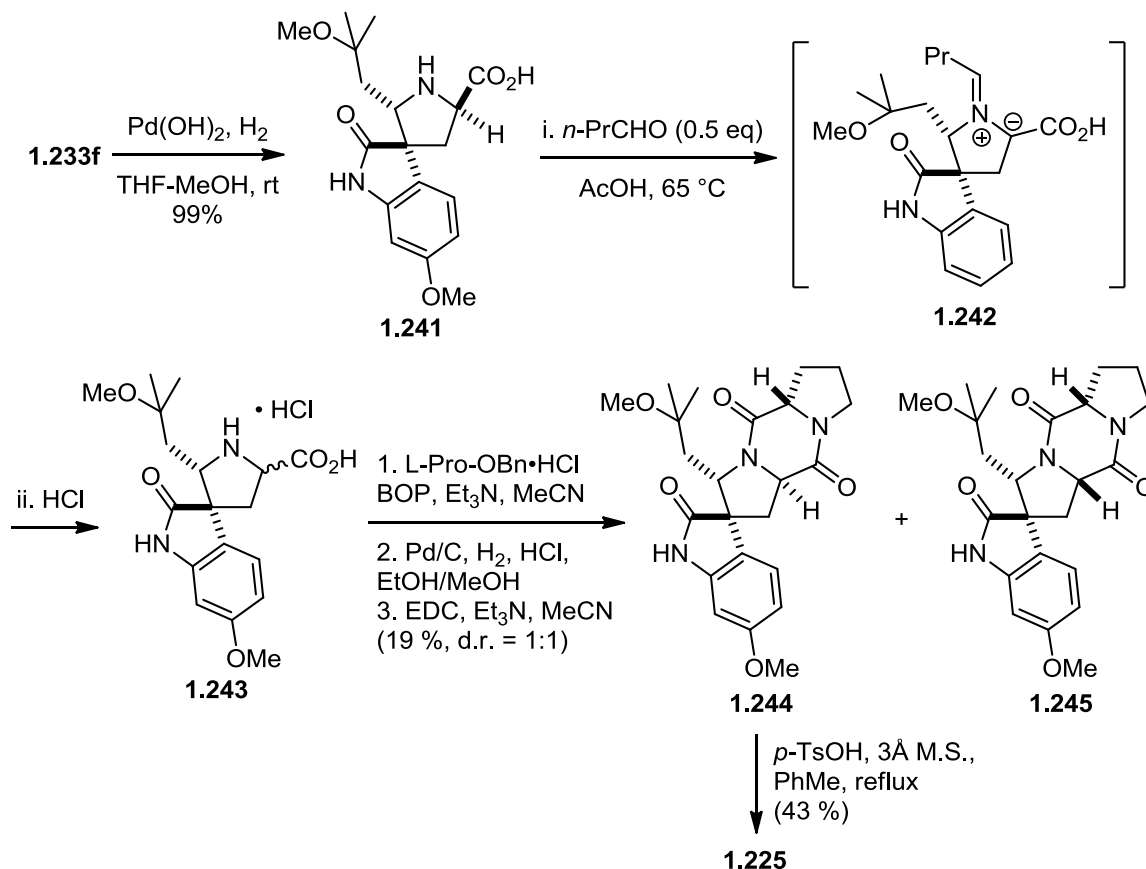
Scheme 1.45. Completion of Spirotryprostatin B (1.226) and 12-*epi*-Spirotryprostatin B (1.240)



The completion of the spirotryprostatin A total synthesis involved the use of yet another azomethine ylide (Scheme 1.46). The chiral auxiliary of **1.233f** was removed by

hydrogenolysis, and the corresponding amino acid was heated with catalytic butyraldehyde to accomplish epimerization of the amino acid stereochemistry via azomethine ylide **1.242** to give a mixture of amino acid diastereomers **1.243**. This mixture was then taken on to construct the final two rings of the natural product to give a mixture (~1:1) of diketopiperazines **1.244** and **1.245** in ~20% over the four step sequence. A final elimination of **1.244** gave spirotryprostatin A (**1.225**) in 9 total synthetic steps and in ~2% overall yield.

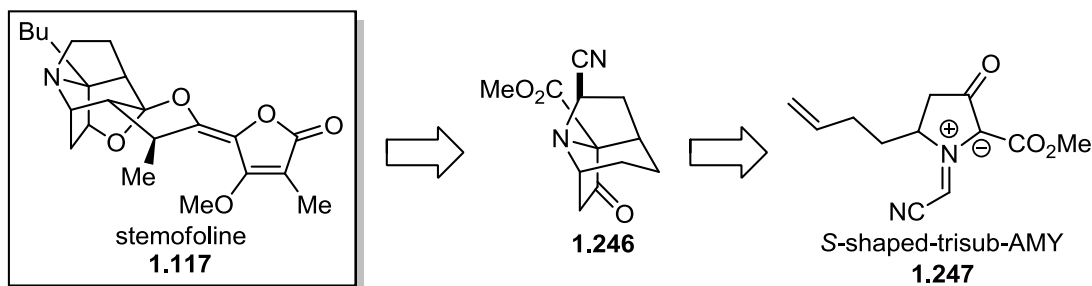
Scheme 1.46. Completion of Spirotryprostatin A Total Synthesis



1.2.4.5 The Stemofoline Alkaloids

The stemofoline alkaloids were isolated from the *Stemona japonica* plant and constitute a series of similarly substituted alkaloids, represented by stemofoline (**1.117**, Scheme 46). As outlined in section 1.2.2.5 in this review, these alkaloids have an impressive array of biological properties. The Martin and Gin groups have reported three separate accounts of the construction of these alkaloids using three separate novel 1,3-DPC methods reactions in the construction of the tricyclic core of these alkaloids (see section 1.2.6.4 for the second Martin group approach and section 1.2.2.5 for the Gin account).^{14, 39-41} The Martin group, in attempting to generate a 1,1-disubstituted azomethine ylide (*nor*-cyano-**1.247**), discovered a novel oxidative azomethine ylide formation, which maintained the cyano function to give the *S*-shaped trisubstituted azomethine ylide **1.247** (Scheme 1.47).³⁹ This ylide reacted in an intramolecular 1,3-DPC reaction with the tethered unactivated olefin to give the tricyclic core **1.246** of the stemofoline alkaloids.

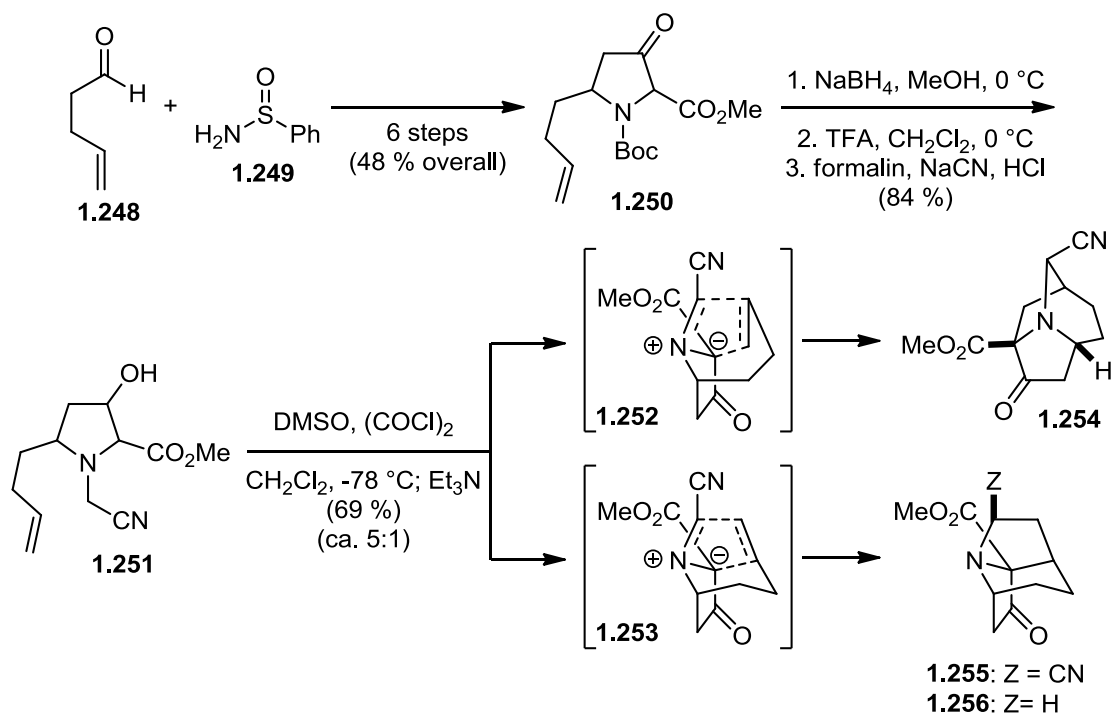
Scheme 1.47. Retrosynthesis of Stemofoline



The first Martin group account began with 1-pentenaldehyde (**1.248**) and sulfonamide **1.249** and employed chemistry developed by Davis for the general synthesis of 5-substituted pyrrolidinones. In this way, pyrrolidinone **1.250** was synthesized over a

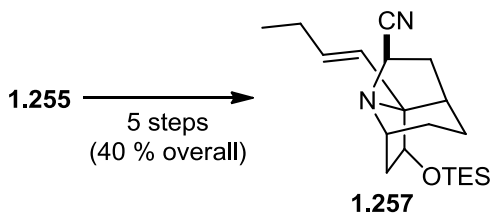
six step sequence in 48% overall yield (Scheme 1.48). Pyrrolidinone **1.250** was refunctionalized to give aminonitrile **1.251** in 84% yield over the three step sequence. The original plan was to expel the cyano group and form an iminium ion, which could undergo deprotonation to give the corresponding azomethine ylide. This transformation proved elusive; however, under Swern oxidation conditions it was discovered that a cycloaddition took place unexpectedly. Interestingly, the cyano function was maintained during the course of the 1,3-DPC, which suggested that the azomethine ylide **1.247** formed via an oxidative iminium ion formation. Since the reaction was inherently basic, the azomethine ylide was formed by deprotonation of the iminium ion, which reacted out of two regioisomeric transition states **1.252** and **1.253** to give a mixture (ca. 5:1) of the corresponding cycloadducts **1.254** and **1.255** in 69% yield. The removal of the cyano-group from **1.255** under a variety of conditions in an attempt to access the *nor*-cyano core **1.256**, however, proved not possible with this intermediate.

Scheme 1.48. 1,3-DPC via Iminium Deprotonation in Stemofoline Partial Synthesis



Cycloadduct **1.255** could be further elaborated to the more advanced tricyclic compound **1.257** bearing the butyl side chain and the appropriate alcohol stereochemistry over a five step sequence (Scheme 1.49). The overall sequence to the fully functionalized stemofoline core **1.257** was thus accomplished in 15 total synthetic steps and in 9% overall yield. Unfortunately, the cyano-group again proved too robust to be removed from the tricyclic core at this stage.

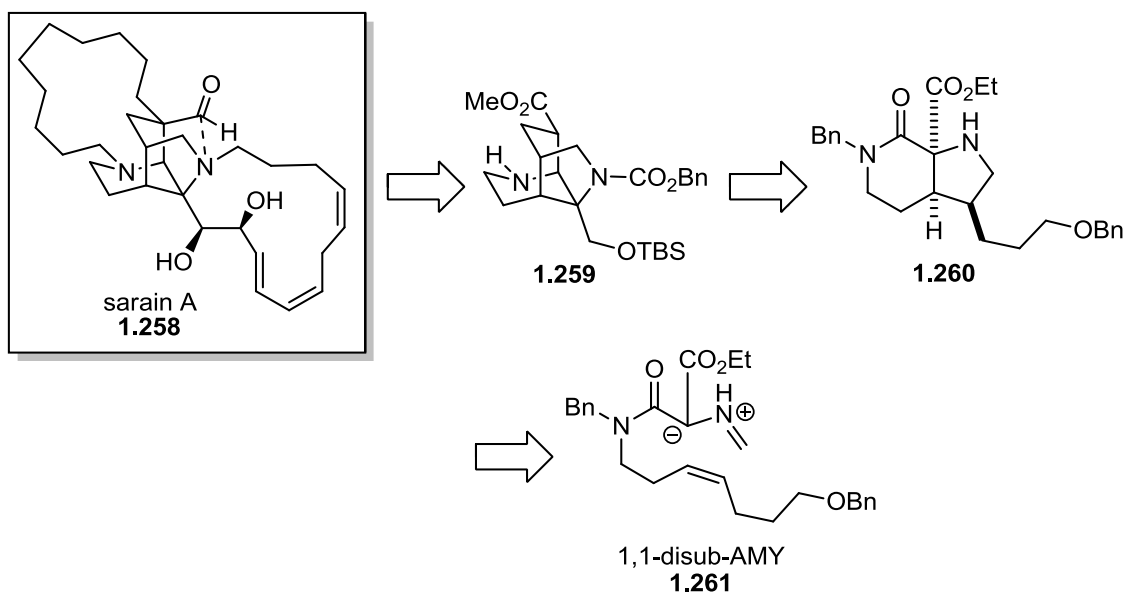
Scheme 1.49. Elaboration of Cycloadduct 1.255 toward Stemofoline



1.2.4.6 *Sarain A*

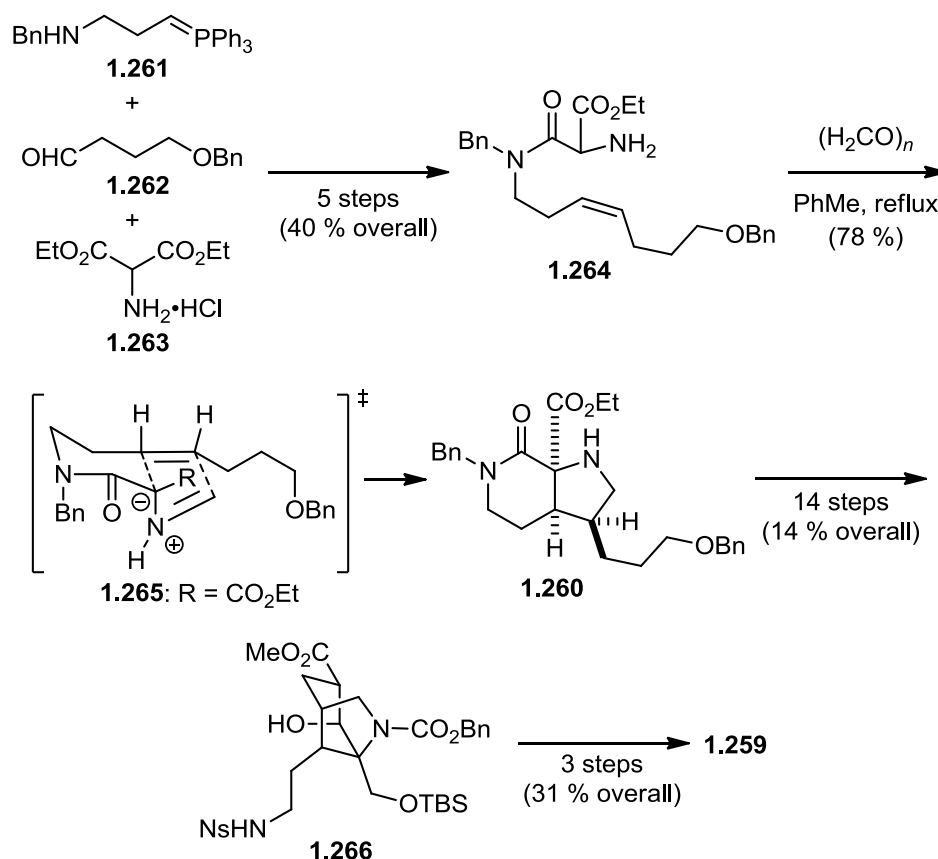
Isolated from the marine sponge *Reniera sarai*, sarain A (**1.258**) has inspired a number of innovative synthetic efforts due to its very unique caged/macrocyclic architecture. Interestingly, as enforced by the rigidity of the caged core structure, the proximal aldehyde and amino residues are bonded causing the sarain alkaloids to exist as zwitterionic-like compounds. The biological activity of the sarain alkaloids also adds to their intrigue, in that they have been shown to exhibit antitumor, antibacterial, and insecticidal activities. There have been three accounts of synthetic efforts towards sarain A involving nearly identical 1,3-DPC strategies, two by Heathcock and another by Weinreb (see section 1.2.6.2 for additional discussion).⁴²⁻⁴⁸ One of the strategies reported by Heathcock involves the formation of the 1,1-disubstituted azomethine ylide **1.261** via iminium deprotonation in the construction of the bicyclic compound **1.260** (Scheme 1.50). This intermediate was thus elaborated into the caged core **1.259** of the sarain alkaloids.

Scheme 1.50. Retrosynthesis of Sarain A



The Heathcock approach began with compounds **1.261**, **1.262**, and **1.263**, which were elaborated into amino ester **1.264** over five total steps (Scheme 1.51).^{46, 49} The desired azomethine ylide **1.261** was then generated by heating the amino ester with paraformaldehyde in refluxing toluene, which underwent an intramolecular 1,3-DPC reaction with the tethered unactivated olefin via the chair-like transition state **1.265** to give the bicycle **1.260** in 78% yield as a single diastereomer. This bicyclic compound was then subjected to a 14 step sequence to prepare the bridged compound **1.266** in 14% overall yield. Elimination of the alcohol followed by removal of the nosyl-protecting group of **1.266** resulted in a Michael reaction, which furnished the caged tricyclic core of sarain A **1.259** thus completing a 23 step partial synthesis of sarain A in ~1% overall yield.

Scheme 1.51. 1,3-DPC via Iminium Deprotonation in Sarain A Partial Synthesis



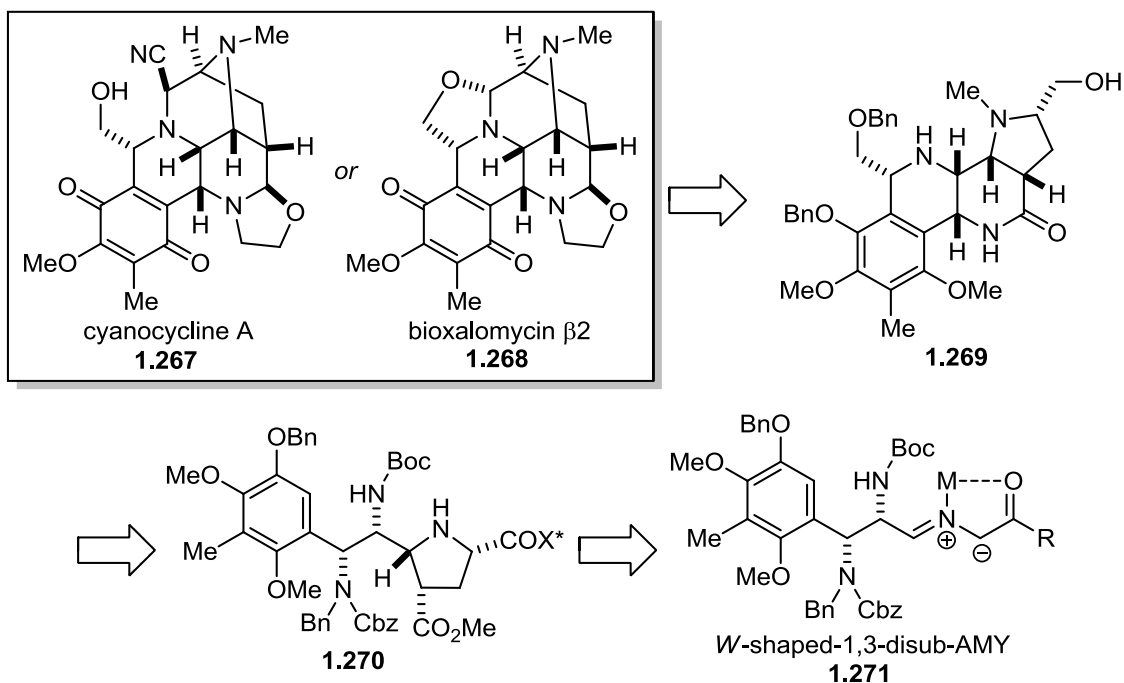
1.2.5 Applications Involving the Ionization of Metalloiminium Ions

1.2.5.1 Cyanocycline A & Bioxalomycin β₂

Structurally similar to the quinocarcin alkaloids (refer to sections 1.2.4.1, 1.2.6.3, and 1.2.7.2 for related discussions of these types of alkaloids), the cyanocycline and bioxalomycin alkaloids have been shown to exhibit broad-spectrum antibiotic and antimicrobial activity. Isolated from *Streptomyces* species, these alkaloids contain a densely fused polycyclic ring system making them attractive targets for chemical synthesis. The Garner group targeted these alkaloids using metallo-azomethine ylide

1.271 (Scheme 1.52).⁵⁰ The ionization of metalloiminium ions deserve special consideration due to subtle differences in reactivity that can lead to different types of pyrrolidine than those directly accessible by the deprotonation of alkyl iminium ions. For one, the chelation ability of most metals capable of forming this type of azomethine ylide can enforce a *W*-shaped ylide leading to 2,5-*syn*-pyrrolidines. Also, these types of ylides hold the promise of catalytic asymmetric techniques by virtue of the tunability of the ligands on the metal center. In this case, however, Garner aimed to employ a chiral auxiliary instead of a chiral metal catalyst to induce asymmetry.

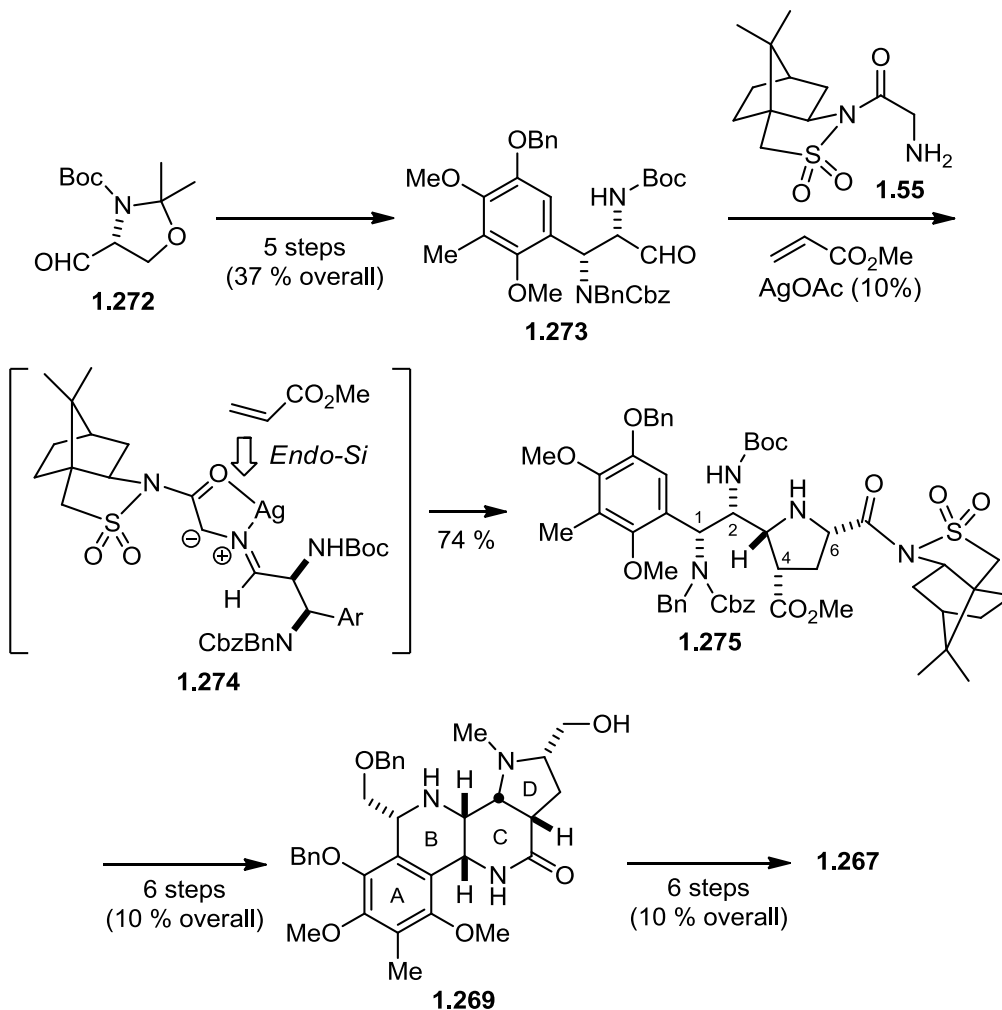
Scheme 1.52. Retrosynthesis of Cyanocycline A



The Garner synthesis began with aldehyde **1.272**, which was elaborated into aldehyde **1.273** in 5 steps and in 37% overall yield (Scheme 1.53). The formation of the metallo-azomethine ylide was conducted with the glycine modified Oppolzer's-L-

camphorsultam chiral auxiliary **1.55** as the amino component, which was condensed with aldehyde **1.273** in the presence of a Ag(I) catalyst to give azomethine ylide **1.274**. Reaction with methyl acrylate via the *endo*-1,3-DPC transition state gave the 2,5-*syn*-pyrrolidine **1.275** in 74%. It is important to note that this type of cycloaddition method, not only provided the *syn*-stereochemistry where most similar azomethine ylide formations give the *anti*-result, but it provided direct access to the NH-substituted pyrrolidine. This can be useful if either direct N-functionalization is required in the synthesis, or if a non-amine protecting group is required for the remainder of the synthesis. Pyrrolidine **1.275** was then elaborated to the tetracyclic compound **1.269** over a six step sequence, which employed the C(1)-amino group to cyclize into the C(4)-ester to construct the C-ring, and the C(2)-amino group to form the B-ring via a Pictet-Spengler reaction. The tetracycle **1.269** was then converted to **1.267** in another 6 steps to constitute a 21 step total synthesis of cyanocycline A in <1% overall yield. Cyanocycline A (**1.267**) has also been shown to be an intermediate in the synthesis of bioxalomycin β 2 (**1.268**), therefore this synthetic effort also constitutes a formal total synthesis of **1.268**.

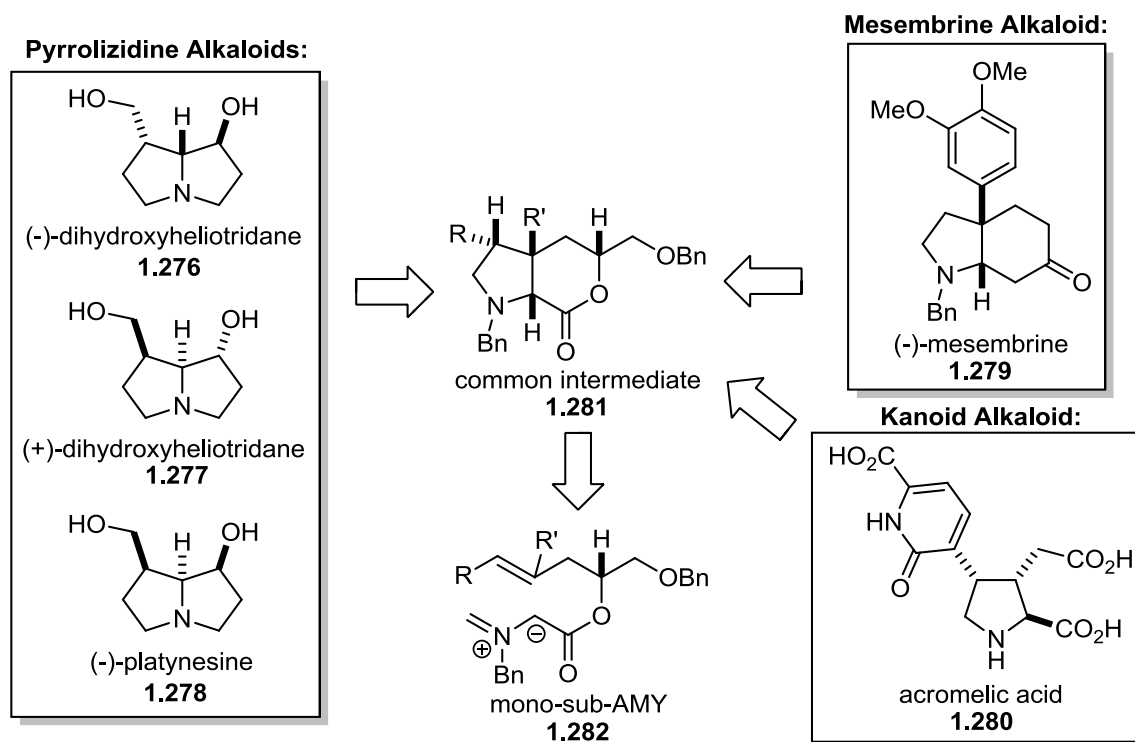
Scheme 1.53. Asymmetric 1,3-DPC via Imine Metallation in Cyanocycline A (1.267)



1.2.6.1 Pyrrolizidine, Kanoid & Mesembrine Alkaloids

activities as glycosidase inhibitors (Scheme 1.54). The kanoid alkaloids, represented here by acromelic acid (**1.280**), have been studied and employed as useful tools in neurobiology due to their ionotropic glutamate receptors agonism properties. Finally, mesembrine (**1.279**) isolated from the South African plant *Sceletium toruosum* (known as Kanna), has been shown to be a serotonin reuptake and PDE4 inhibitor, and is thought to contribute to the antidepressant effect of natural Kanna. While these alkaloids have little in common, the Ogasawara group has developed a 1,3-DPC strategy, which allowed access to a common class of bicyclic intermediates of type **1.281**, which have proved viable intermediates in the syntheses of all of these alkaloids (Scheme 1.54).⁵¹⁻⁵⁴ A similar disconnect is outlined in Section 1.2.4.6 and 1.2.6.2 toward the synthesis of sarain A. Azomethine ylides of type **1.282** were accessed via thermolysis of the corresponding aziridines

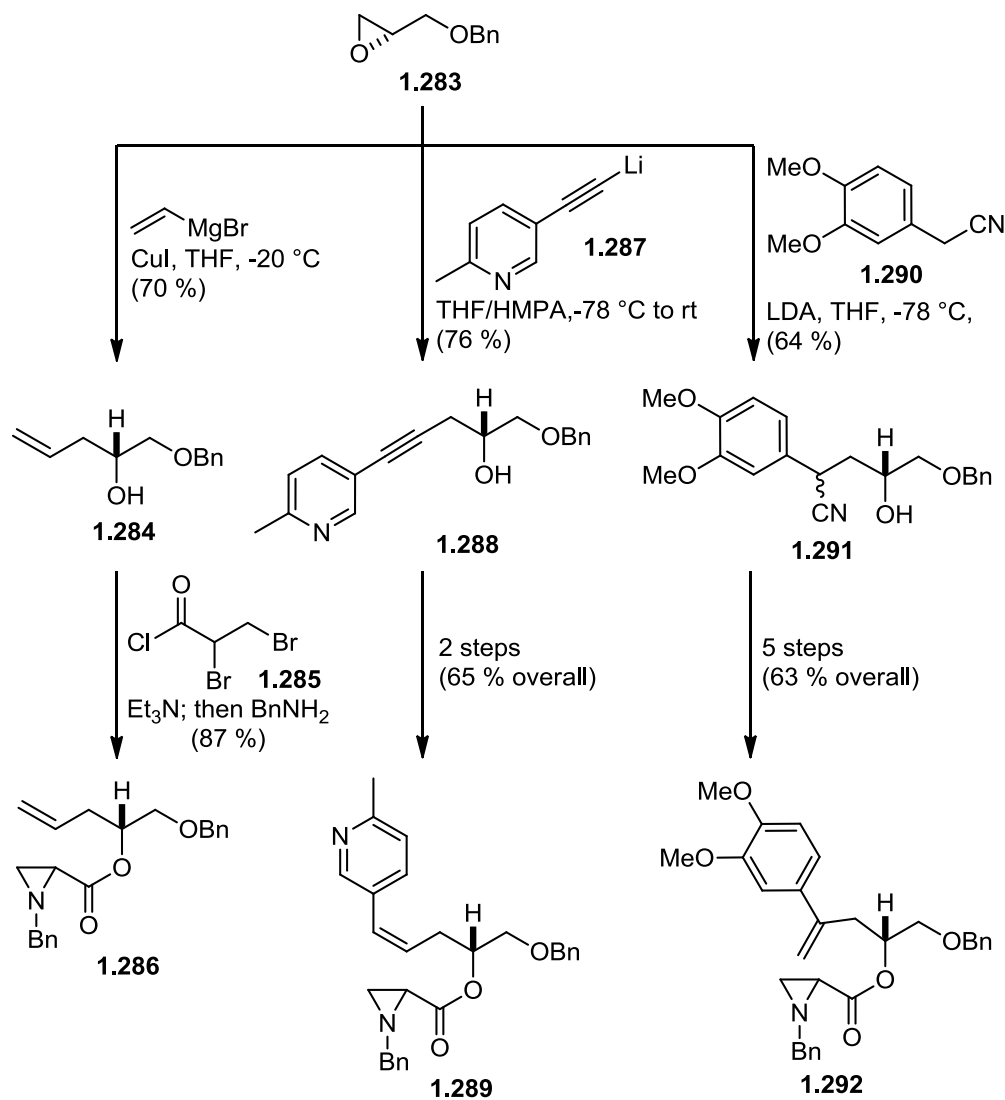
Scheme 1.54. Asymmetric 1,3-DPC via Aziridine Thermolysis in Pyrrolizidine, Kanoid & Mesembrine Alkaloid Total Syntheses



In order to access the common bicyclic intermediates **1.281**, Ogasawara developed a common synthetic strategy to synthesize the various aziridines required for the cycloaddition reaction starting with chiral epoxide **1.283** (Scheme 1.55). Addition of the appropriate carbon nucleophile (Grignards, lithium acetylides, and nitrile anions all proved competent) gave the corresponding alcohol products. For the pyrrolizidine alkaloids, vinyl magnesium bromide was used to give the homoallylic alcohol **1.284** in 70% yield. This alcohol was then functionalized to install the acylaziridine component by acylation of the alcohol with acid chloride **1.285**, followed by double alkylation of

benzyl amine with the resulting dibromide to give the aziridine **1.286** in 87% yield (Scheme 1.55).

Scheme 1.55. Synthesis of Aziridine Starting Materials using a General Strategy



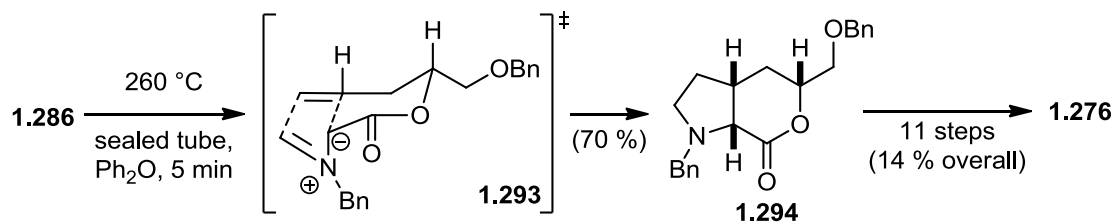
For acromelic acid, the pyridyl lithium acetylide **1.287** was used to open epoxide **1.283** to give homopropargyl alcohol **1.288** in 76% yield. The alkyne was then reduced to the trans-homoallylic alcohol then the acylaziridine moiety was installed in the same

fashion as described above using reagent **1.285** to give aziridine **1.289** in 65% over the two step sequence (Scheme 1.55).

Finally for mesembrine, the nitrile anion of **1.290** opened **1.283** to give the cyano-compound **1.291** in 64% yield. The benzonitrile group was then converted to the corresponding styrene moiety and the resulting homoallylic alcohol was functionalized in the same fashion using reagent **1.285** to give aziridine **1.292** in 63% yield over the five step sequence (Scheme 1.55).

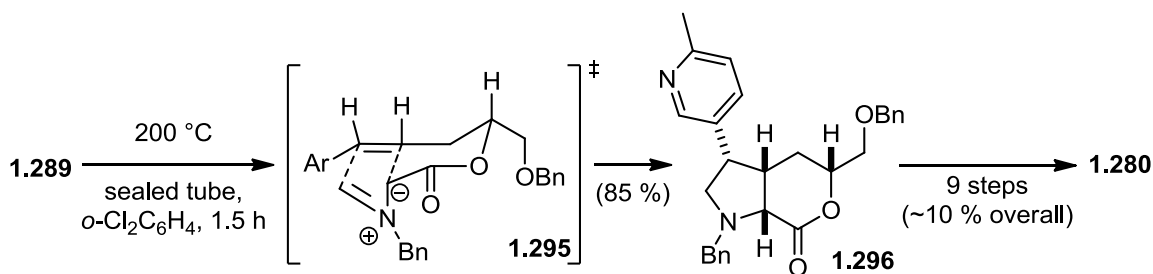
With aziridine **1.286** in hand, the syntheses of the various pyrrolizidine alkaloids could be advanced using an intramolecular 1,3-DPC reaction (Scheme 1.56). Thermolysis of aziridine **1.286** resulted in an azomethine ylide which reacted via the chair-like transition state **1.293** to give the bicyclic lactone **1.294** in 70%. This type of transition state model works to describe each of the following cycloaddition reactions for explaining the resulting stereochemical outcome in each case. Bicycle **1.294** was subsequently converted into (-)-dihydroxyheliotridane (**1.276**) in an additional 11 steps and 14% overall yield. The (+)-enantiomer **1.277** and (-)-platynesine (**1.278**) were also synthesized using comparable synthetic methods to that described for **1.276**. The total asymmetric synthesis of **1.276** was thus accomplished in 14 total synthetic steps and in 6% overall yield.

Scheme 1.56. Asymmetric 1,3-DPC via Aziridine Thermolysis in (-)-Dihydroxyheliotridane Total Synthesis



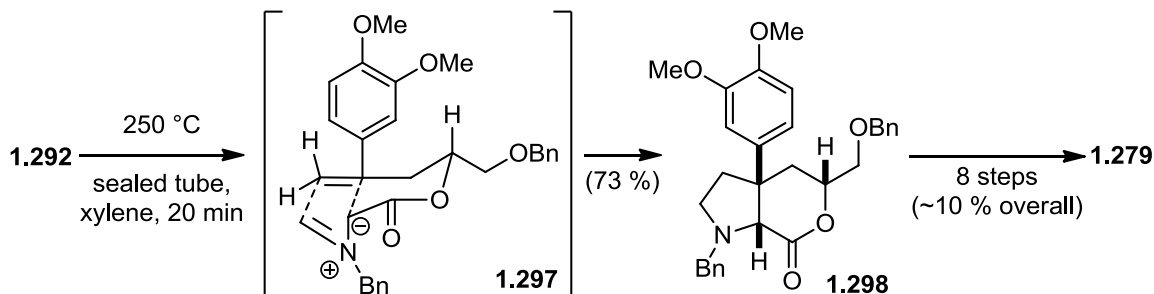
The preparation of aziridine **1.289**, set up the completion of the synthesis of acromelic acid (Scheme 1.57). The thermolysis of **1.289** resulted in an azomethine ylide, which reacted with the tethered unactivated olefin via transition state **1.295** to give the bicyclic lactone **1.296** in 85% as a single diastereomer. Lactone **1.296** was then converted to acromelic acid (**1.280**) in an additional 9 steps in just under 10% overall yield. The total synthesis of acromelic acid was thus accomplished in 13 total synthetic steps and in ~4% overall yield.

Scheme 1.57. Asymmetric 1,3-DPC via Aziridine Thermolysis in Acromelic Acid Total Synthesis



In a similar fashion as described above, aziridine **1.292** was subjected to thermolysis to give an azomethine ylide, which reacted with the appended olefin via the transition state **1.297** to give cycloadduct **1.298** in 73% yield as a single diastereomer (Scheme 1.58). The bicyclic lactone **1.298** was then advanced to mesembrine (**1.279**) in an additional 8 steps and in approximately 10% yield. The total synthesis of mesembrine was accomplished completed in 15 total synthetic steps and in ~3% overall yield.

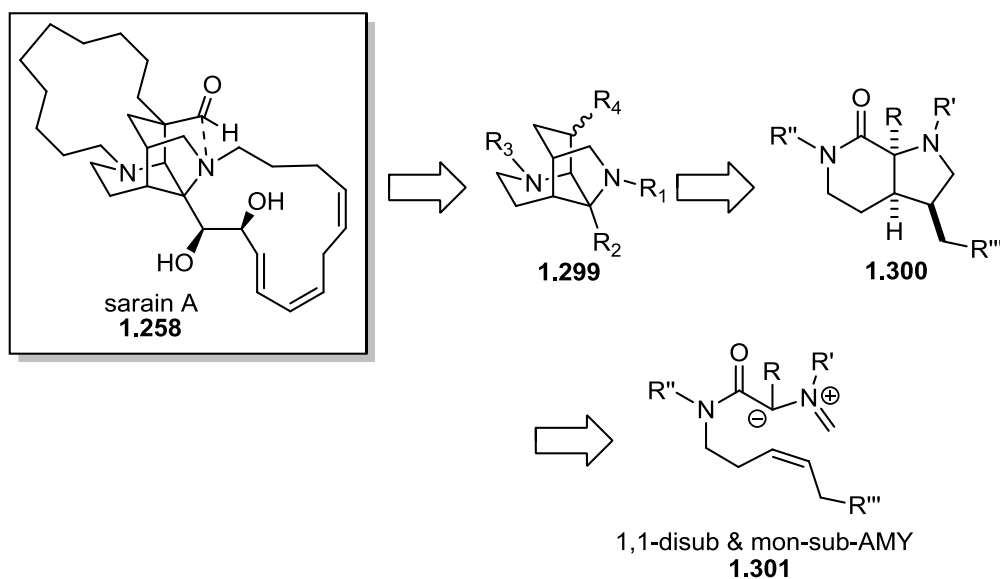
Scheme 1.58. Asymmetric 1,3-DPC via Aziridine Thermolysis in Mesembrine Total Synthesis



1.2.6.2 Sarain A

Sarain A (**1.258**) was isolated from the marine sponge *Reniera sarai*, and as outlined in section 1.2.4.6 of this review, these alkaloids have an impressive array of biological properties and a very unique architecture. A synthetic approach involving aziridine thermolysis to access azomethine ylide **1.301** was developed almost simultaneously by both the Weinreb and Heathcock groups, and both approaches studied essentially the exact same cycloaddition reaction to prepare the bicyclic lactam of type **1.300** as an intermediate in the synthesis of the tricyclic core of sarain A (Scheme 1.59).

Scheme 1.59. Retrosynthesis of Sarain A

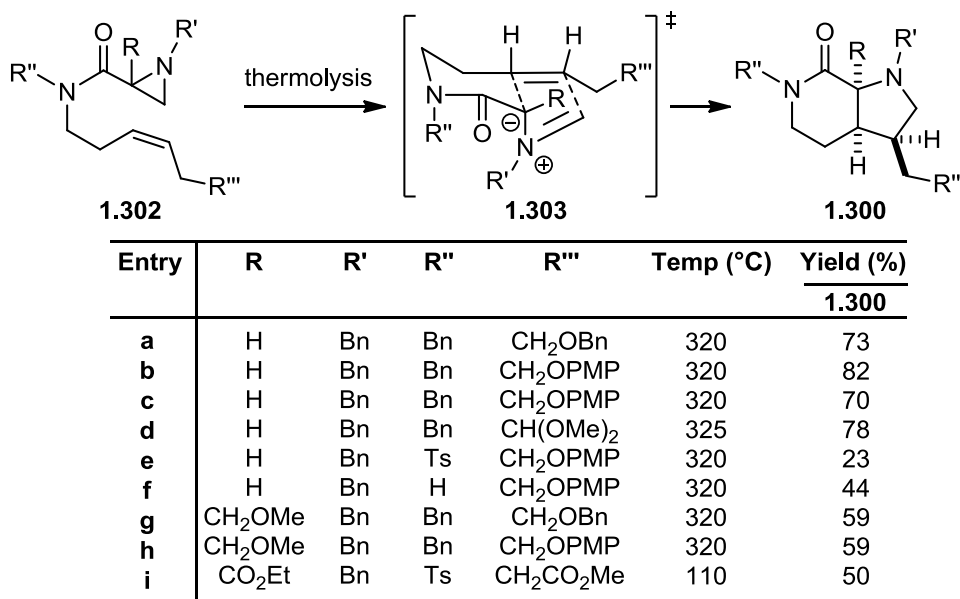


A series of aziridine amides **1.302^{xx}** were synthesized by both the Weinreb (Scheme 1.60, entries a-h) and Heathcock groups (Scheme 1.60, entry i), and tested in the key intramolecular 1,3-DPC.^{42, 43, 45, 47, 48} Thermolysis of the aziridines of type **1.302** gave azomethine ylides, which underwent intramolecular 1,3-DPC reactions with the tethered unactivated olefins via the transition state of type **1.303** to give the bicyclic lactams **1.300**. In all cases the protecting group on the aziridine nitrogen (R') was a benzyl group, however, a fairly extensive screen of the other substituents was performed. In the examples where the lactam nitrogen was an alkyl group ($R''=\text{Bn}$) the 1,3-DPC consistently gave higher yields. It is notable that when the lactam was unsubstituted ($R''=\text{H}$) a majority of what was isolated from the reaction was cyclization of the lactam nitrogen into the iminium ion of the azomethine ylide. This can be explained by the less favorable *S-trans* conformation of the amide being required for the cycloaddition (see

^{xx} Aziridine **1.302d** was synthesized in 6 steps from dihydroanisole and N-benzyl-2-aziridine carboxylic acid in 44% overall yield. Aziridine **1.302i** was synthesized in 11 steps from ethyl malonate and cyclohex-4-enone in ~9% overall yield.

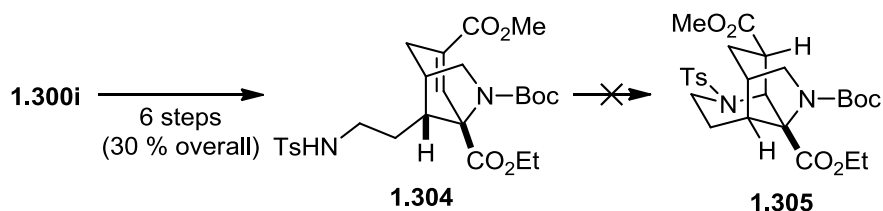
Section 1.2.3.3 for a similar discussion). The cycloaddition also seemed to tolerate a wide array of olefinic side chains and even an acetal functional group (entry d). When the aziridine was further substituted at the R-group to give 1,1-disubstituted ylides, however, the reaction yields were far less favorable. It is noteworthy that in the case where the azomethine ylide was further stabilized with a dicarbonyl substitution (entry i, R=CO₂Et) that the temperature required to achieve complete conversion was much lower than the other examples.

Scheme 1.60. 1,3-DPC via Aziridine Thermolysis in Sarain A Partial Synthesis



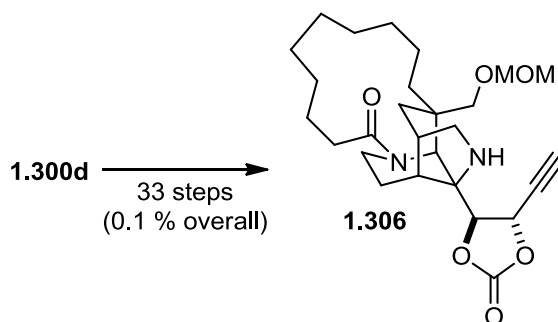
Heathcock used the cycloadduct **1.300i** to advance to the enoate **1.304** using a 6 step synthetic sequence; however, the targeted Michael reaction to construct the tricyclic sarain core was unsuccessful with the N-tosyl compound (Scheme 1.61). In later efforts, the Heathcock group advanced this synthetic approach using an N-nosyl group, and by applying a modified cycloaddition method (see Section 1.2.4.6 in this review for further discussion).

Scheme 1.61. Heathcock – Attempt to Advance Cycloadduct to Sarain Core



Weinreb applied cycloadduct **1.300d** toward the advancement of their synthetic efforts (Scheme 1.62). In an additional 33 steps (0.1% overall yield), the tetracyclic compound **1.306** was synthesized bearing the fully functionalized caged core and the western macrocyclic ring of sarain A. The Weinreb partial synthesis of sarain A was thus accomplished in 40 total synthetic steps and in <0.01% overall yield.

Scheme 1.62. Weinreb – Advancement of Cycloadduct in Sarain A Partial Synthesis

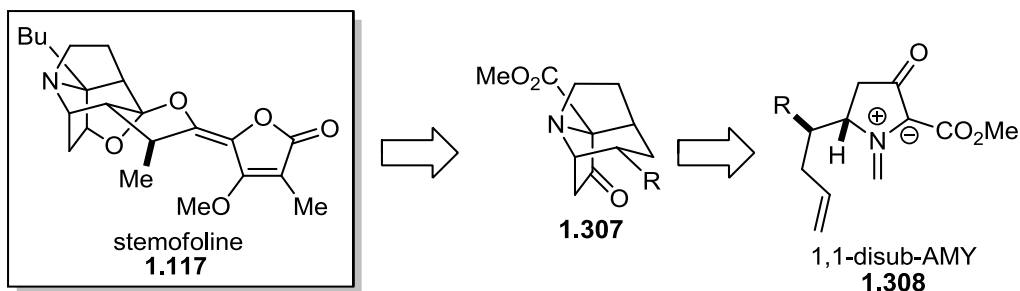


1.2.6.3 The Stemofoline Alkaloids

The stemofoline alkaloids were isolated from the *Stemona japonica* plant and constitute a series of similarly substituted alkaloids, represented by stemofoline (**1.117**, Scheme 64). As outlined in section 1.2.2.5 in this review, these alkaloids have an impressive array of biological properties. The Martin and Gin groups have reported three separate accounts of the construction of these alkaloids using three separate novel 1,3-

DPC methods reactions in the construction of the tricyclic core of these alkaloids (see section 1.2.4.5 for the first Martin group approach and section 1.2.2.5 for the Gin account). The second generation approach reported by the Martin group, targeted the 1,1-disubstituted azomethine ylide **1.308** as a reactive intermediate in the construction of the stemofoline core **1.307** (Scheme 1.63).⁴⁰ The targeted azomethine ylide was envisioned coming from the thermolysis of a 2,2-unsubstituted oxazolidine following precedent from the Joucla group.^{55, 56}

Scheme 1.63. Retrosynthesis of Stemofoline

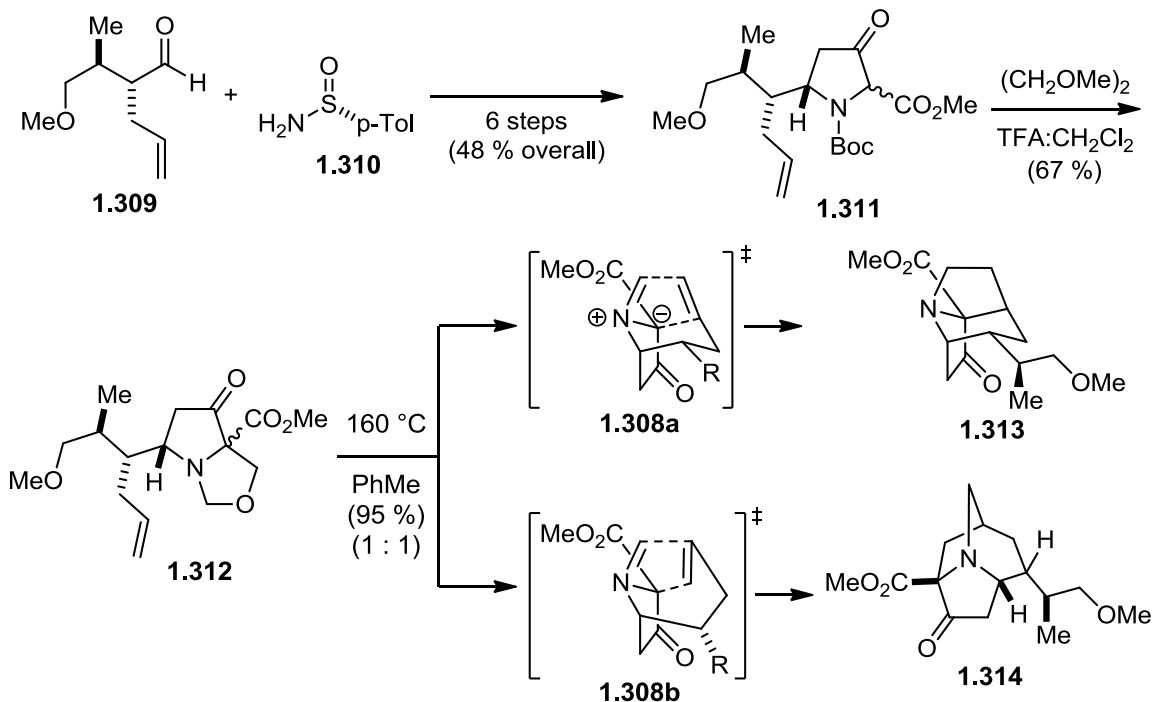


The modified Martin approach began with aldehyde **1.309**^{xxi} and chiral sulfonamide **1.310**, which were subjected to a general strategy developed by Davis for the preparation of 5-substituted pyrrolidinones, to access pyrrolidine **1.311** over a 6 steps sequence (Scheme 1.64). With pyrrolidinone **1.311** in hand, oxazolidine **1.312** was synthesized in 67% yield by treatment with excess TFA and dimethoxymethane. Cognizant of a method developed by Joucla for the preparation of azomethine ylides from the thermolytic decomposition of oxazolidines, they subjected oxazolidine **1.312** to similar thermolytic conditions to generate the azomethine ylide **1.308**. This ylide reacted via two regioisomeric transition states **1.308a** and **1.308b** to give a mixture (1:1) of

^{xxi} Synthesized in 6 steps from 4-methoxycrotonic acid in 45% overall yield.

regioisomeric cycloadducts **1.313** and **1.314** in 95% yield. Recall from the previously discussed Martin group cycloaddition (Section 1.2.4.5), that a very high regioisomeric ratio was obtained when the azomethine ylide was substituted at the termini with a cyano-group, the presence of the cyano group was problematic for advancing the total synthesis due to its robust nature. This approach by the Martin group aimed to access a *nor*-cyanated stemofoline core in an asymmetric fashion; however, in now accessing the *nor*-cyanated ylide **1.308** the corresponding cycloaddition was far less regioselective. It is noteworthy that an advanced and appropriately functionalized tricyclic core of the stemofoline alkaloids **1.313** was obtained in asymmetric fashion in 15 total synthetic operations and in an impressive 7% overall yield (see Chapter 2 & 3 in this dissertation for a more in-depth discussion of this work).

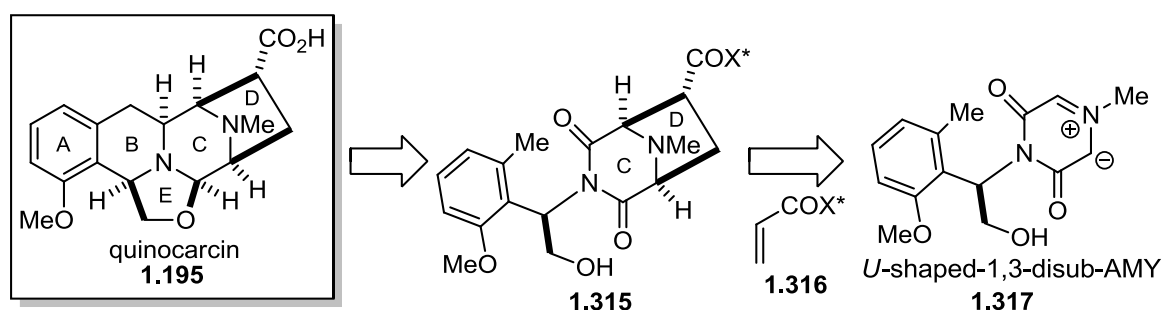
Scheme 1.64. 1,3-DPC via Oxazolidine Thermolysis in Stemofoline Partial Synthesis



1.2.6.4 Quinocarcin

Quinocarcin (**1.195**) is a natural secondary metabolite isolated from *Streptomyces melanovinaceus*, which has been shown to exhibit antimicrobial and anti-tumor activities (See Sections 1.2.4.1, 1.2.5.1, & 1.2.7.2 for related discussions of this and related alkaloids). The previous synthesis discussed in this review by Williams (Section 1.2.4.1) sought to construct the D-ring of the quinocarcin alkaloids via a 1,3-DPC. Through their efforts, the concept of using a cyclic azomethine ylide to enforce the *U*-shaped geometry was successfully applied to construct the bridged azabicycle. A similar strategy was adopted by Garner where the ylide **1.317**, constituting the C-ring of quinocarcin, was used to construct the bridged azabicyclic scaffold **1.315** (Scheme 1.65).^{32, 57-61} Garner's approach, however, was to use an aziridine photolysis as a way to access the targeted azomethine ylide, and to perform the cycloaddition in an asymmetric fashion. The preparation of **1.315** set up the construction of the remaining ABE rings.

Scheme 1.65. Retrosynthesis of Quinocarcin

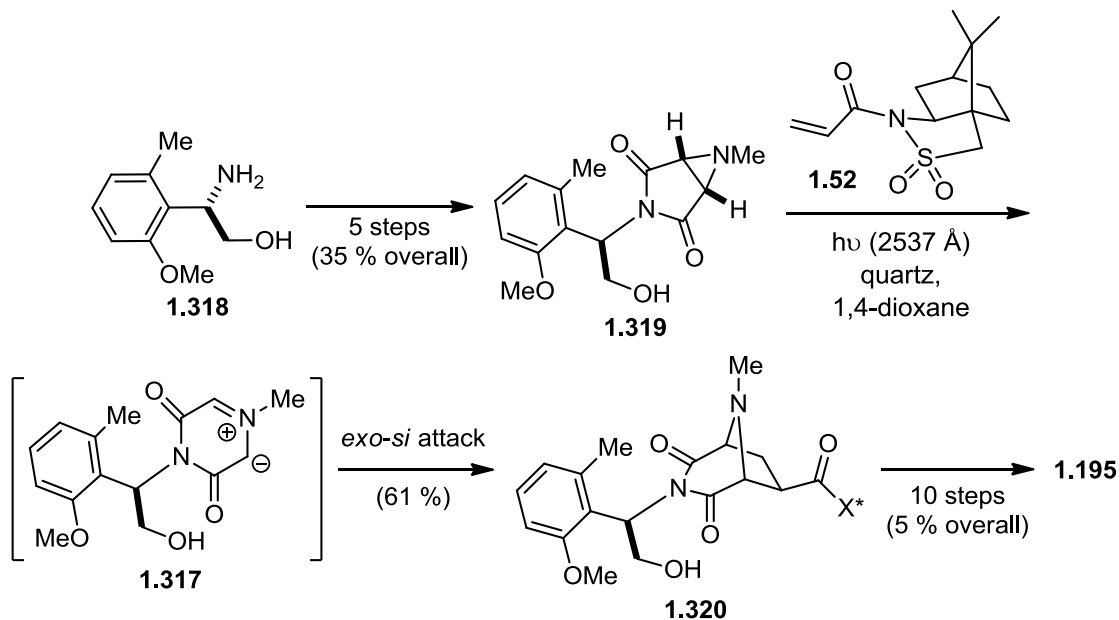


Garner's approach began with chiral amino alcohol **1.318**^{xxii}, which was converted to the bicyclic aziridine **1.319** in 5 steps, 35% overall yield (Scheme 1.66). Next, the aziridine **1.319** was subjected to photolysis at 2537 Å in a quartz vessel to give

^{xxii} Synthesized in 8 steps from 2-methoxy-6-methylbenzaldehyde in 29% overall yield.

the corresponding azomethine ylide **1.317**. Initial model studies of the key cycloaddition reaction aimed to study the reaction parameters necessary to give, not only high *exo*-selectivity, and high diastereoselectivity relative to the benzylic stereocenter. These initial studies bore out the necessity of using a chiral dipolarophile, namely the Oppolzer's sultam modified acrylic acid **1.52**. Attempts to use methyl acrylate in the cycloaddition led to good yields of the desired *exo*-products; however the benzylic stereocenter had no impact on the facial selectivity, delivering a mixture (1:1) of diastereomers. The approach of tethering the dipolarophile to the benzylic alcohol side chain was also investigated, unfortunately a similar lack of facial selectivity was observed. The use of Lewis acid additives/catalysts was also investigated to effect the stereoselectivity, however the Lewis acid/base adducts led to complex reaction mixtures due to the incompatible photophysical properties of these adducts under the required irradiation conditions. Thus, the use of the chirally modified dipolarophile **1.52** was necessary to control the facial selectivity; and, in the event, the reaction of aziridine **1.319** and **1.52** delivered the azabicycle **1.320** in 61% yield via the *exo-si* mode. A further 10 synthetic operations were then required to convert cycloadduct **1.320** into quinocarcin, thus completing a 24 step total synthesis in <0.1% overall yield.

Scheme 1.66. Asymmetric 1,3-DPC via Aziridine Photolysis in Quinocarcin Total Synthesis



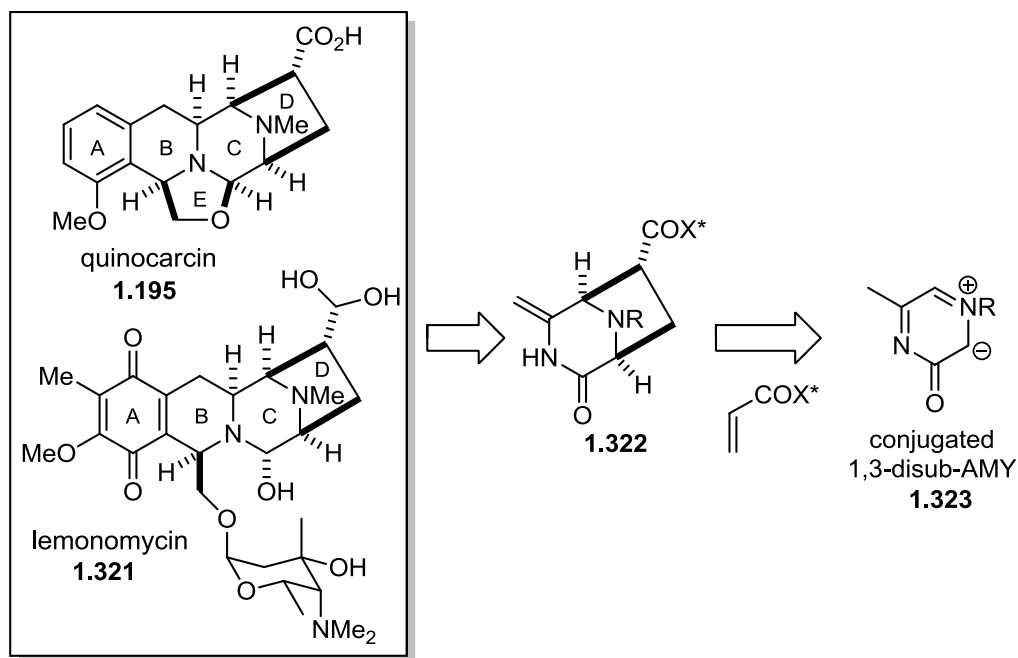
1.2.7 Applications Involving Conjugated Azomethine Ylides via Oxopyridinium & Oxopyrizinium Ions

1.2.7.1 (-)-Quinocarcin/(-)-Lemonomycin: Conjugated Azomethine Ylide via Oxo Pyrazinium Salt

Quinocarcin (**1.195**) and related alkaloid lemonomycin (**1.321**), isolated from *Streptomyces* species, have been shown to exhibit antimicrobial, antibiotic and anti-tumor activities (See sections 1.2.4.1, 1.2.5.1, & 1.2.6.4 for discussions of these and related alkaloids). The previous syntheses discussed in this review for quinocarcin by Williams (Section 1.2.4.1) and Garner (Section 1.2.6.4) sought to construct the D-ring of the quinocarcin via an intermolecular 1,3-DPC. Through their efforts, the concept of using a cyclic azomethine ylide to enforce the *U*-shaped geometry was successfully applied to

construct the bridged azabicyclic portion of this molecule. Furthermore, Garner employed the Oppolzer sultam-derived acrylamide **1.52** to control the diastereoselectivity of the cycloaddition event to effect an asymmetric synthesis. This disconnect was also adopted by Stoltz in his own syntheses of quinocarcin and lemomycin, however Stoltz aimed to use a cycloaddition method originally developed by Joule which employed a oxopyrizinium ion **1.323** in an intermolecular 1,3-DPC cycloaddition reaction with a chirally modified dipolarophile (Scheme 1.67).^{62, 63} Cycloadduct **1.322**, bearing the C and D rings of the target alkaloids would then serve as a common intermediate in the total syntheses of both quinocarcin and lemomycin.

Scheme 1.67. Retrosynthesis of Quinocarcin (1.195) and Lemomycin (1.321)

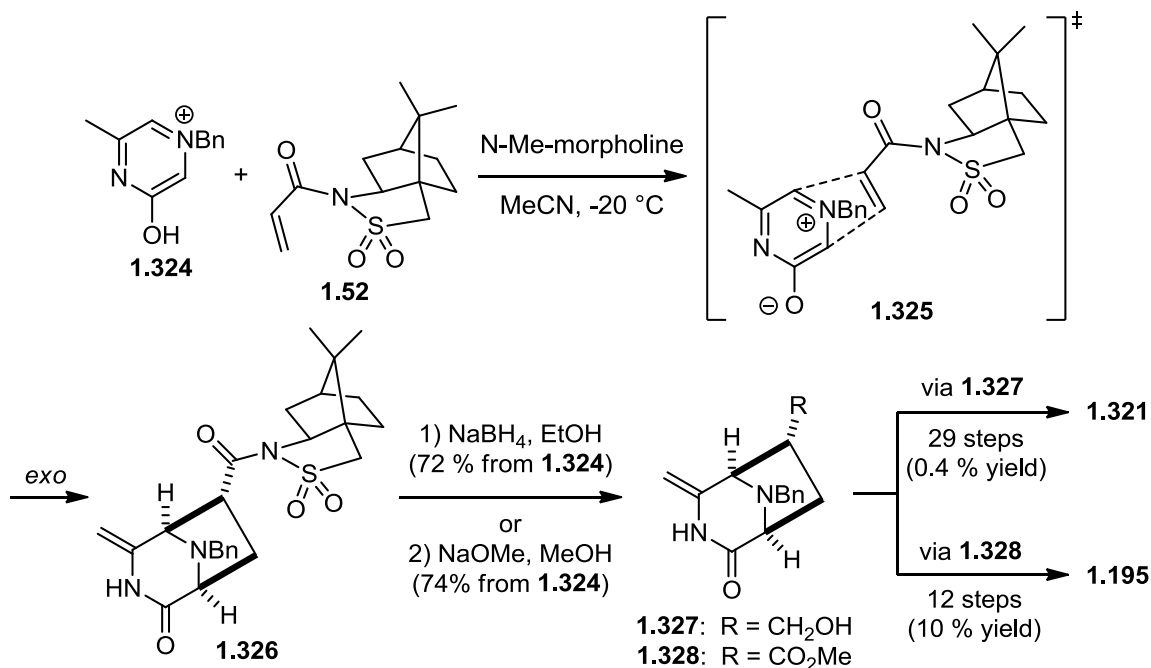


Stoltz's synthetic efforts began with the bromo pyrizium salt **1.324**, which was quickly elaborated into the target bridged azabicyclic compound **1.326** by treatment with acrylamide **1.52** and N-methyl morpholine to effect an asymmetric intermolecular 1,3-

DPC reaction via **1.325** (Scheme 1.68). The cycloaddition reaction proceeded with great *exo*-selectivity (a common outcome of the Oppolzer sultam dipolarophile) and with high diastereoselectivity to give the enantiomerically enriched **1.326**. This intermediate was used in the synthesis of quinocarcin by treatment with sodium methoxide to give methyl ester **1.328** in 72% yield from **1.324**. The synthesis of quinocarcin (**1.195**) was completed over a 14 step total synthesis and in 7% overall yield.

The synthesis of the considerably more complicated lemonomycin was accomplished by using **1.326**. In this case, treatment of **1.326** with sodium borohydride gave alcohol **1.327** in 74% yield from **1.324**. An additional 29 steps were then required to complete the total synthesis of lemonomycin in <0.1% overall yield.

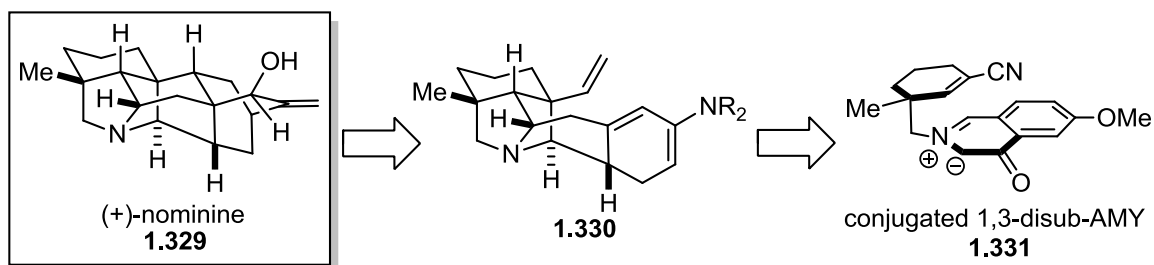
Scheme 1.68. Asymmetric 1,3-DPC via Oxopyridinium Ylide in Quinocarcin (1.195) and Lemonomycin (1.321) Total Syntheses



1.2.7.2 (+)-Nominine: Conjugated Azomethine Ylide via Oxo-Pyridinium Salt

Nominine (**1.329**) belongs to a diverse class of alkaloids known as the hesitine products, which have been isolated across a number of genera of plants including: *Aconitum*, *Consolida*, *Delphinium*, *Rumex*, and *Spiraea*, which have all been widely used in traditional herbal medicine. The hesitine alkaloids exhibit an array of biological activities *in vivo*, including potent vasodilating, antiarrhythmic, immunomodulating, and analgesic properties. These alkaloids are structurally unique due to their highly functionalized and densely caged architectures, making them intriguing synthetic targets. In that vein, the Gin group designed a synthetic approach to (+)-nominine (**1.329**) using an intramolecular 1,3-DPC of the conjugated oxopyridinium ion **1.331** with a tethered activated olefin (Scheme 1.69).^{64, 65} This 1,3-DPC would set up a subsequent intramolecular Diels-Alder reaction of **1.330** later in the synthesis that would lead to the fully caged nominine core.

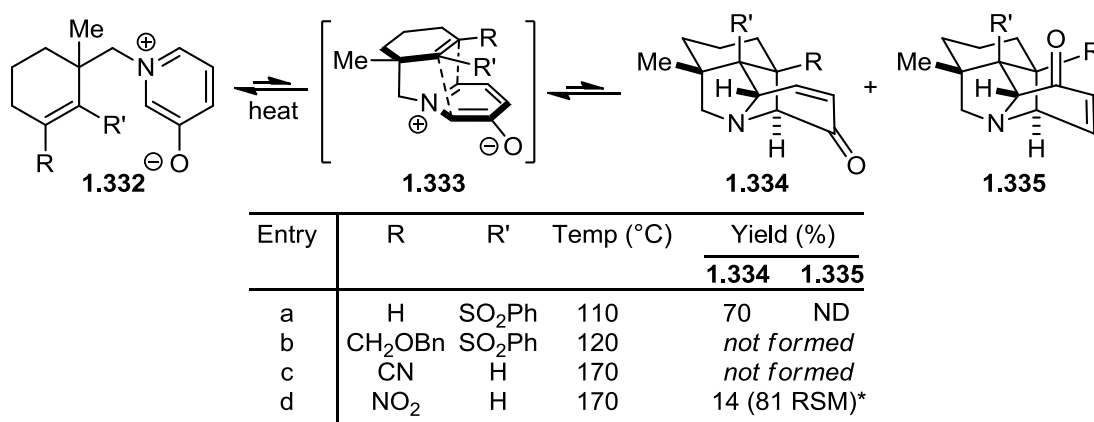
Scheme 1.69. Retrosynthesis of (+)-Nominine



The Gin approach first began with a cursory investigation of the guiding principles of the intramolecular cycloaddition reaction of simple oxopyridinium ions of type **1.332** (Scheme 1.70). It was necessary to know the correct substitution of the dipolarophilic portion of the molecule that would lead to the best distribution of regioisomers **1.334** and **1.335**, with cycloadduct **1.335** being the desired product.

Unfortunately, these initial systems did not give the desired product due to an inherent preference for the wrong regioisomer. It was also discovered that the cycloadducts themselves, at the high temperature of the cycloaddition conditions, were formed reversibly and, in fact, under the reaction conditions, typically favored the starting materials.

Scheme 1.70. Initial Screening of a Suitable Substrate Array for Critical 1,3-DPC



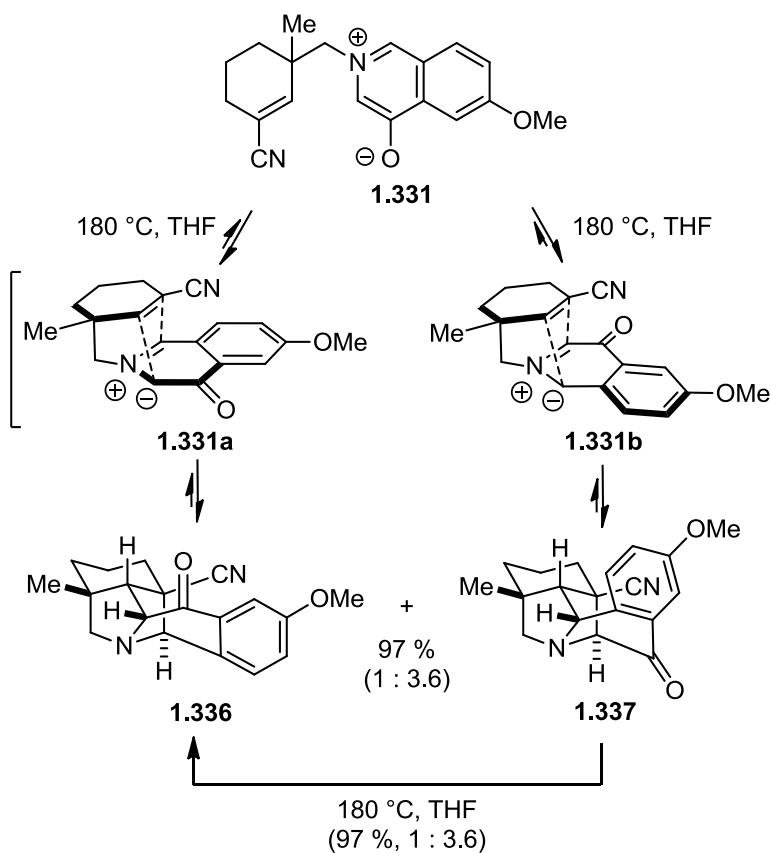
The next approach was to investigate the use of the bezofused analogues **1.331**, in the hope that the cycloadducts formed from this reaction would be more thermodynamically stable (Scheme 1.71). As such, the thermolysis of oxopyridinium **1.331**^{xxiii} facilitated an intramolecular 1,3-DPC via regioisomeric transition states **1.331a** and **1.331b** to give a mixture (1:3.6) of cycloadducts **1.336** and **1.337** in 97% yield, favoring the undesired. The ratio (1:3.6) of cycloaddition products represents the mixture at thermodynamic equilibrium, which was subsequently exploited for recycling the major undesired product **1.337** into the desired cycloadduct **1.336**. Resubjecting the isolated undesired cycloadduct **1.337** to the reaction conditions thus led to another mixture (1:3.6)

^{xxiii} Synthesized in 8 steps from *p*-anisaldehyde dimethyl acetal and 3-methylcyclohexeneone in 23% overall yield.

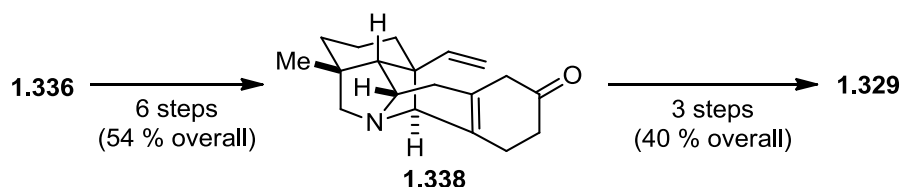
of **1.336** and **1.337**. While this process was less than optimal, it did provide the functionalized core of nominine **1.336** in fairly short order.

With cycloadduct **1.336** in hand, Gin completed the synthesis of nominine by first accessing vinyl compound **1.338** over a 6 step sequence (Scheme 1.72). Treatment of ketone **1.338** with pyrrolidine gave rise to an electron rich dienamine, which underwent an intramolecular Diels-Alder reaction to give the fully caged nominine core. Two additional steps were then required to finish the synthesis of nominine in 19 total synthetic steps and in 2% overall yield (counting the added yield of one recycling step of the undesired cycloadduct).

Scheme 1.71. Asymmetric 1,3-DPC in (+)-Nominine Total Synthesis



Scheme 1.72. Completion of the Total Synthesis of Nominine



1.3 CONCLUSION

The reactions of azomethine ylides have proven a reliable way to construct complex molecular architectures of a variety of classic alkaloids for organic synthesis. These methods continue to find applications, not only as a way to construct basic pyrrolidine ring systems, but to anchor the synthesis of complex caged scaffolds through tandem, intramolecular processes. Despite the huge body of work on this class of reaction, there continues to be novel methods developed to address the formation of azomethine ylides from a continually evolving set of different starting materials. For the most part, a majority of these methods have not yet found application in natural product total synthesis, which provides a plentiful area for groups to explore new chemistries in the future. The application and development of catalytic, asymmetric techniques to the formation and implementation of chiral azomethine ylides is also still underutilized in the field of natural products. Also, the preparation of unstabilized azomethine ylides is sometimes problematic; as such, new general methods for addressing the formation and implementation of these types of ylides are still in demand.

One of the most valuable aspects of the 1,3-dipolar cycloaddition of azomethine ylides is the ability of this reaction class to form four stereocenters simultaneously in a very convergent and highly controlled fashion. Furthermore, with only a rudimentary understanding of the control elements of these reactions, the stereochemical and

regiochemical aspects can generally be predicted accurately before the embarkation of a total synthesis. Depending on the substitution and stereochemistry that is desired, the choice of azomethine ylide and the manner in which the ylide is generated is a crucial first decision in designing a synthetic plan.

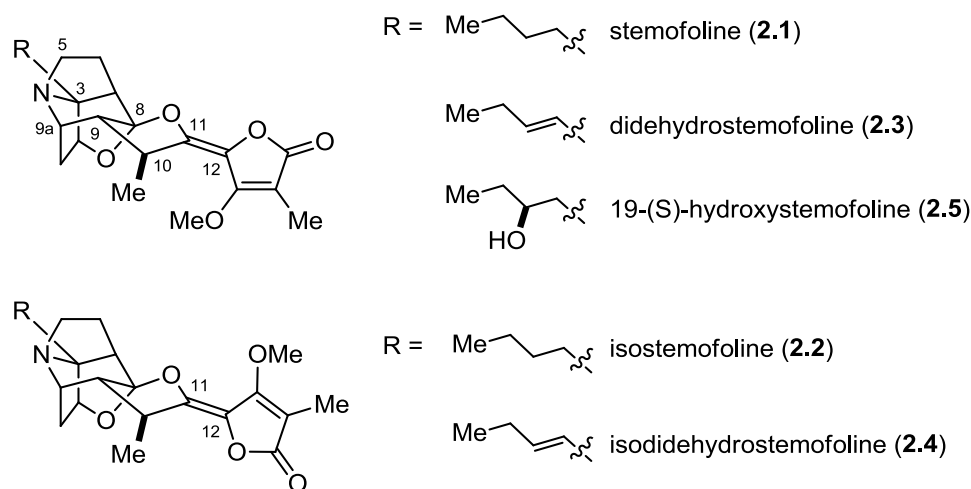
Chapter 2 – The Stemofoline Alkaloids

2.1 INTRODUCTION

2.1.1 Isolation & Biological Activity

The *Stemonaceae* family contains approximately 30 different species of flowering plants native to various regions of Southeast Asia, from which a plethora of biologically active natural products have been isolated.⁶⁶ The ground up leaves and tuberous roots of these plants have been used for centuries in traditional Asian medicine to prepare herbal teas in the treatment of chronic cough symptoms associated with respiratory diseases such as bronchitis and tuberculosis. Additionally, these extracts can be applied as pesticidal remedies in both human and agricultural infestations. The stemofoline alkaloids in particular, exhibit this high insecticidal activity, a consequence of their action as insect acetylcholine receptor antagonists.^{67, 68} Additionally, they exhibit activity against various human carcinoma cell lines and *in vivo* anti-oxytocin activity, with **2.3** being the most potent in both cases.⁶⁹⁻⁷¹ Extensive investigations into the active principles of these plants have revealed a wealth of important alkaloids that pose distinct challenges to chemical synthesis, the greatest of which is presented by the stemofoline alkaloids (Figure 2.1). The first of these alkaloids, didehydrostemofoline (**2.3**), was isolated from the *Stemona japonica* species in 1970 and has since been joined by a family of alkaloids bearing the same caged hexacyclic architecture varying only in the oxidation of the C(3)-side chain and the geometry of the C(11)/C(12) olefin (Figure 2.1).^{66, 67, 69, 70, 72}

Figure 2.1 Selected Stemofoline Alkaloids



The unique structural complexity of the stemofoline alkaloids has inspired numerous synthetic efforts, culminating in two total syntheses. Kende reported the first total synthesis of (±)-isostemofoline (2.2) in 1999,⁷³ which was then followed by the Overman total syntheses of (±)-didehydrostemofoline (2.3) and (±)-isodidehydrostemofoline (2.4) in 2003.⁷⁴ Of the partial synthetic efforts, Thomas reported an approach to stemofoline (2.1) in 1992⁷⁵ and has followed up with two subsequent reports on progress towards these alkaloids.^{76, 77} Gin has also divulged efforts towards stemofoline in 2002,¹⁵ along with a subsequent follow up.¹⁴

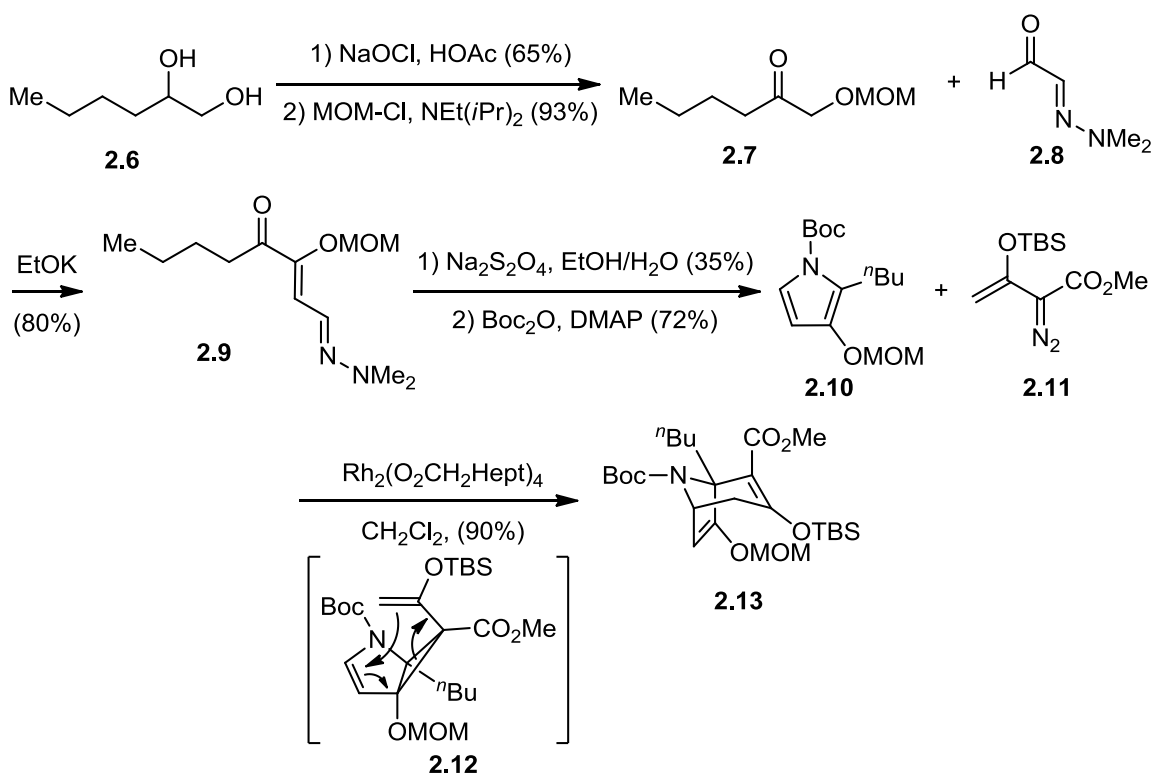
2.1.2 Synthetic Approaches to the Stemofoline Alkaloids

2.1.2.1 Kende Total Synthesis

In 1999 Kende reported the total synthesis of isostemofoline (2.2), which focused on the construction of the full hexacyclic structure utilizing a cascade cyclization approach (Scheme 2.1).⁷³ The early steps of the total synthesis were used to assemble an

initial bridged azabicyclic motif relying on a formal [4+3] cycloaddition of pyrrole **2.10** and known vinyl diazo compound **2.11** (Scheme 2.1). To set the stage for the initial cycloaddition, compound **2.10** was synthesized by first selectively oxidizing diol **2.6** with NaOCl in 65% yield, and protecting the primary alcohol as its methoxymethyl (MOM) ether to afford ketone **2.7** in 93% yield. A Knoevenagel condensation between **2.7** and aldehyde **2.8** afforded the conjugated pyrrole precursor **2.9** in 80% yield. The synthesis of **2.10** concluded with a low yielding cyclization of **2.9**, followed by a Boc-protection of the resulting pyrrole to provide **2.10** in 72% yield.

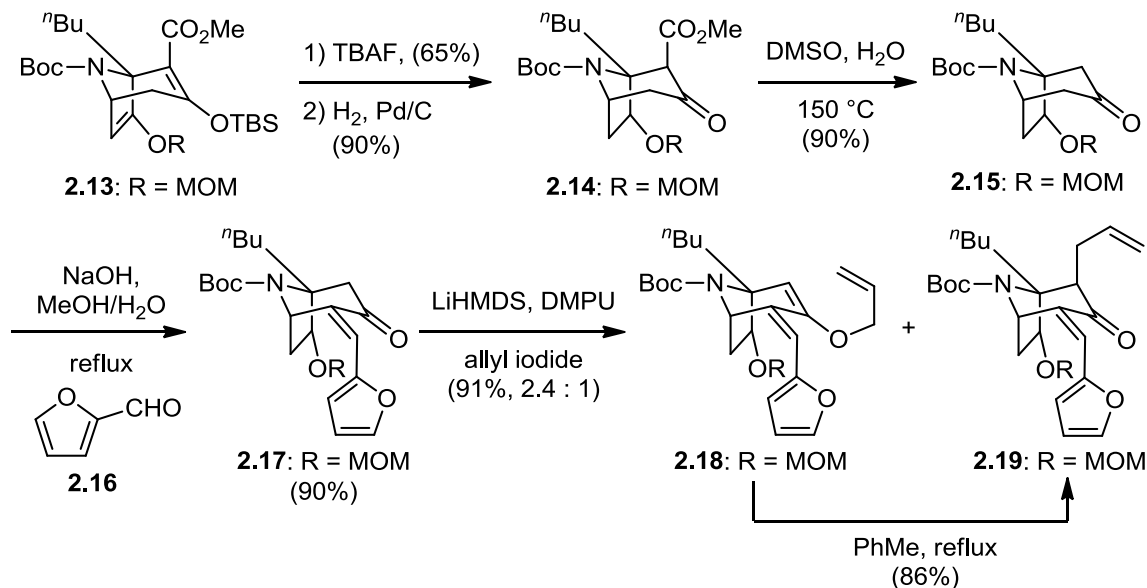
Scheme 2.1



With compound **2.10** in hand, a modification of cycloaddition chemistry developed by Davies was applied.⁷⁸ In this reaction a rhodium catalyzed

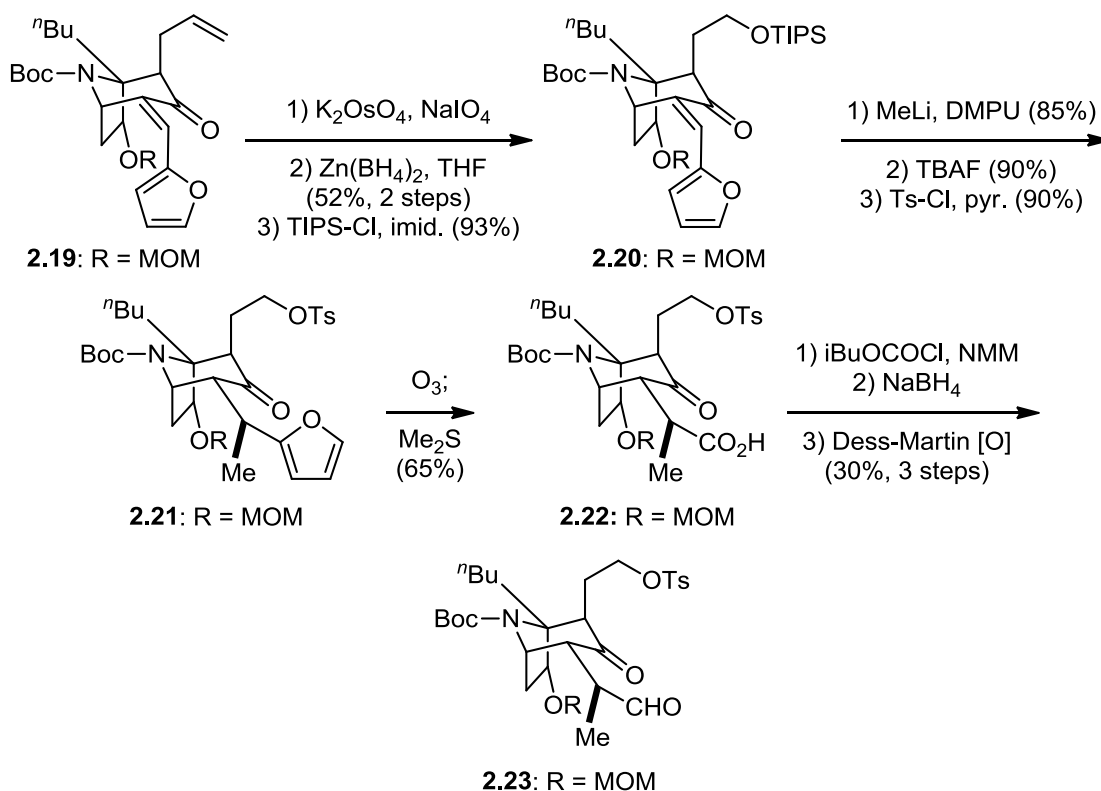
cyclopropanation of the more electron rich side of the pyrrole with vinyl diazo compound **2.11** followed by a Cope rearrangement of intermediate **2.12** resulted in a formal [4+3] cycloaddition to yield the bridged azabicyclic compound **2.13** in 90% yield (Scheme 2.1).

Scheme 2.2



Removal of the silyl enol ether of **2.13** with TBAF proceeded in 65% yield, and hydrogenation gave β -ketoester **2.14** in 90% yield (Scheme 2.2). A subsequent Krapcho decarboxylation of **2.14** gave ketone **2.15** in 90% yield. With **2.15** in hand, a two-step alkylation sequence was used to install the remaining carbon framework for the pentacyclic core of the stemofoline alkaloids. A Knoevenagel condensation of **2.15** with 2-furfural (**2.16**) followed by an allylation with LiHMDS and allyl iodide gave a mixture (2.4:1) of *O*- and *C*-alkylated products **2.18** and **2.19** in 91% yield. A subsequent Claisen rearrangement of the *O*-alkylated product provided an 86% yield of the desired *C*-alkylated product **2.19**.

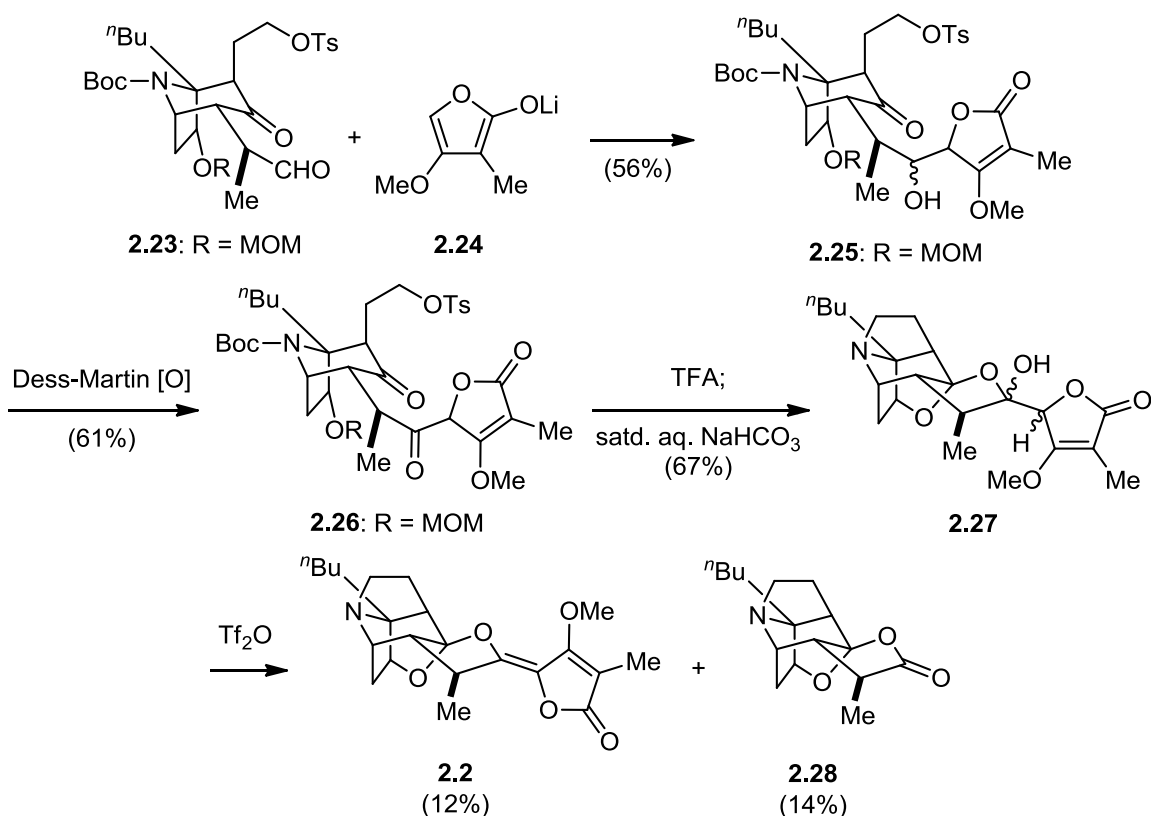
Scheme 2.3



The terminal alkene of **2.19** was converted to the TIPS-protected alcohol **2.20** by first subjecting **2.19** to Johnson-Lemieux conditions followed by selective reduction of the resulting aldehyde with zinc borohydride gave an intermediate alcohol in 52% yield over two steps (Scheme 2.3). Protection of the primary alcohol as its TIPS ether proceeded in 93% yield to give enone **2.20**. In order to set the critical C(10)-methyl stereocenter, a conjugate addition of MeLi in DMPU was performed on enone **2.20** and gave an 85% of the desired C(10)-epimer as the only product. The primary silyl protecting group was removed with TBAF, and the free alcohol was converted to the primary tosylate providing **2.21** in 90% yield. Ozonolysis of the furan side chain of **2.21** gave carboxylic acid **2.22** in 65% yield. A three step sequence was then employed to

convert the carboxylic acid of **2.22** into the required aldehyde **2.23** via reduction of its mixed anhydride in 30% over the three steps.

Scheme 2.4



Installation of the butenolide side chain was accomplished by the aldol reaction of aldehyde **2.23** with the lithium furanone anion **2.24** to deliver an inconsequential mixture of alcohol diastereomers **2.25** in 56% yield (Scheme 2.4). Oxidation of the diastereomeric alcohols **2.25** with Dess-Martin periodinane provided ketone **2.26** in 61%, thereby setting the stage for a key cascade cyclization reaction facilitated by trifluoroacetic acid. Subjecting the bisprotected compound **2.26** to TFA resulted in concomitant Boc- and MOM-deprotection and initiated the desired key cascade reaction.

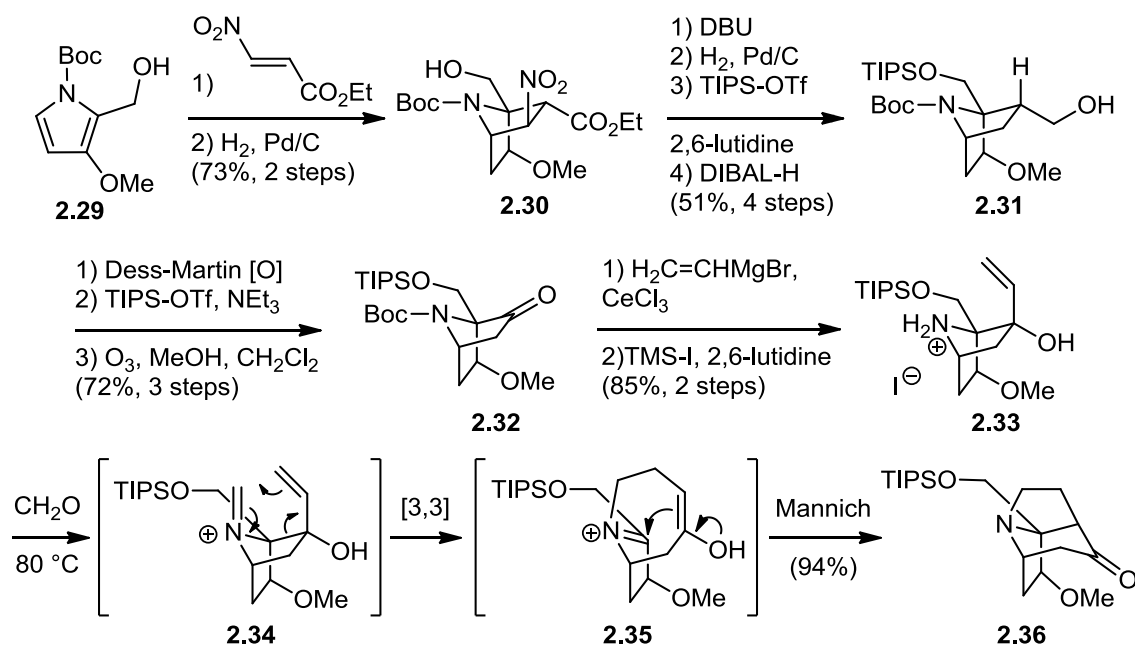
In the event, the resulting free amine cyclized in an S_N2 fashion onto the axially disposed tosyl electrophile, and the resulting free alcohol underwent an acetalization cascade by cyclization into the C(8)-ketone then into the pendant ketone resulting in a 67% yield of the pentacyclic lactol **2.27**. At this stage, all that remained to complete the synthesis was the dehydration of lactol **2.27**; this step, however, proved problematic resulting in either no product or a majority of the retro-aldol product **2.28** under a variety of conditions. The use of triflic anhydride as the dehydrating agent, however, did provide a 12% yield of isostemofoline (**2.2**) culminating in a 26 step total synthesis in an overall yield of 0.007%.

2.1.2.2 Overman Total Synthesis

The Overman total synthesis of (±)-didehydrostemofoline (**2.3**) and (±)-isodidehydrostemofoline (**2.4**), which was reported in 2003, sought to employ a cascade aza-Cope/Mannich approach to the azatricyclic natural product core (Scheme 2.5). Starting with a Diels-Alder cycloaddition between pyrrole **2.29** and ethyl-(*E*)-3-nitroacrylate followed by hydrogenation of the resulting enol ether gave the desired cycloadduct **2.30** in a two-step yield of 73% along with 13% of the undesired regioisomer. Elimination of the β-nitro group of **2.30** was accomplished with DBU and resulted in an enoate that was further reduced by hydrogenation. The primary alcohol was protected as its TIPS ether, and the ester was reduced with DIBAL to furnish alcohol **2.31** in 51% yield over the four step sequence. Oxidation of alcohol **2.31** using Dess-Martin periodinane gave an intermediate aldehyde that was elaborated into its corresponding TIPS silyl enol ether in an additional step. Ozonolysis of the intermediate silyl enol ether gave ketone **2.32** in 72% yield over three steps. Reaction of ketone **2.32**

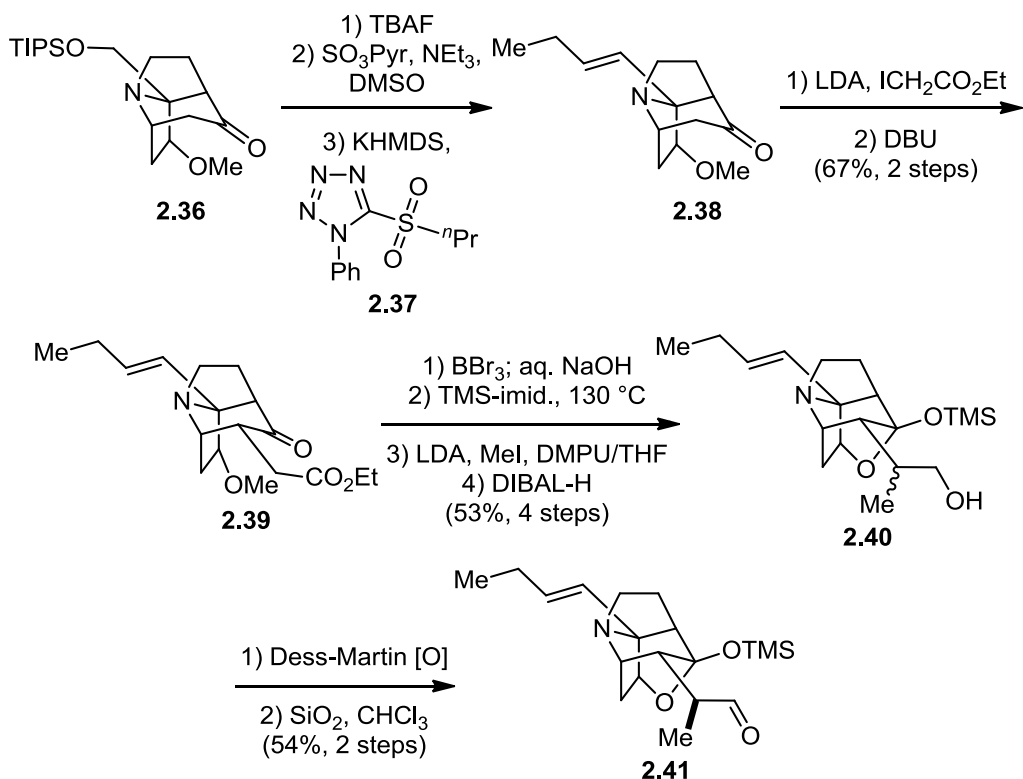
with vinyl magnesium bromide followed by Boc-deprotection with TMS-I gave ammonium salt **2.33** in 85% yield over two steps.

Scheme 2.5



With **2.33** in hand, the key tandem aza-Cope/Mannich reaction could be performed to set up the tricyclic core of the stemofoline alkaloids (Scheme 2.5). Heating **2.33** with paraformaldehyde resulted in an intermediate iminium ion **2.34**, which underwent the envisioned aza-Cope rearrangement to give iminium ion **2.35**. The resulting iminium ion then underwent an intramolecular Mannich reaction with the adjacent enol ether to afford tricyclic ketone **2.36** in 94% yield.

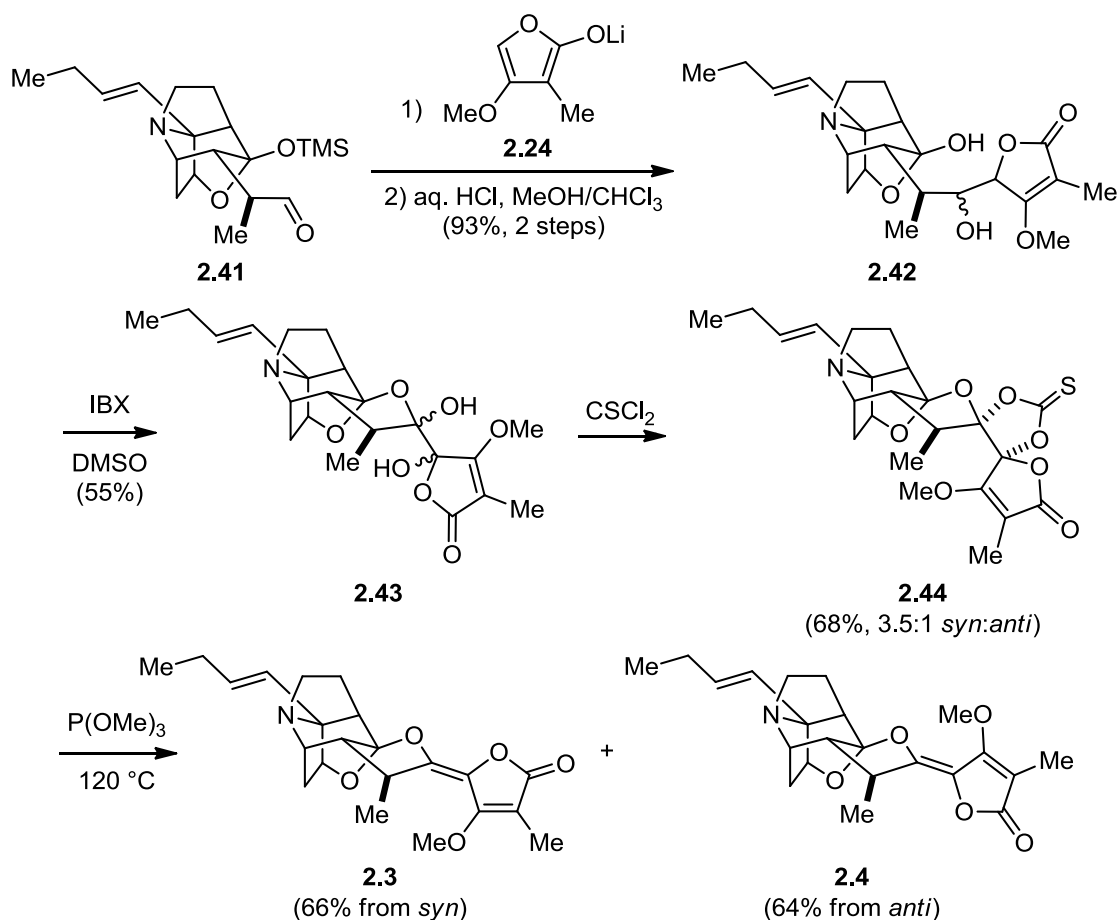
Scheme 2.6



Ketone **2.36** was then subjected to a three step protocol to install the necessary butenyl side chain (Scheme 2.6). This sequence commenced with a silyl deprotection of **2.36** which provided a primary alcohol that was oxidized under Parikh-Doering conditions to the corresponding aldehyde. Finally a Julia-Kochi olefination of the intermediate aldehyde with **2.37** gave olefin **2.38** with the required butenyl side chain in 70% yield over three steps. Alkylation of **2.38** with ethyl iodoacetate provided the axially substituted product, which was equilibrated with catalytic DBU to provide a 67% yield of the desired equatorially substituted ketone **2.39**. Formation of the first lactol ring was then accomplished by treating the methyl ether **2.39** with BBr_3 , which also induced cyclization, and the resulting lactol was protected as the TMS ether in an additional step.

Alkylation of the ester side chain with iodomethane to install the C(6)-methyl group, followed by a subsequent DIBAL reduction, gave alcohol **2.40** in 53% yield over four steps. Dess-Martin oxidation of **2.40** gave the corresponding aldehyde as a diastereomeric mixture, which could be equilibrated on silica gel to give primarily the desired epimer **2.41** in 54% yield over two steps.

Scheme 2.7



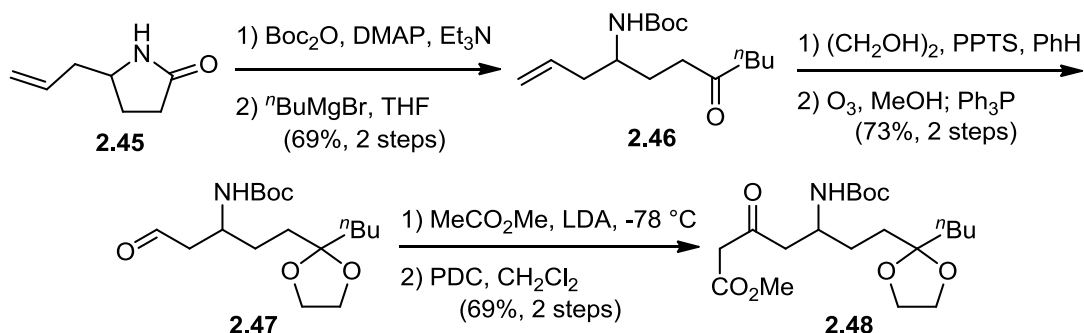
With aldehyde **2.41** in hand, the butenolide moiety was installed by an aldol reaction with lithium furanone **2.24**, followed by hydrolysis of the TMS protecting group to furnish lactol **2.42** in 93% yield over two steps (Scheme 2.7). Oxidation of alcohol

2.42 with IBX facilitated the formation of the final lactol ring as well as γ -oxidation of the butenolide moiety to give diol **2.43** in 55% yield. In order to complete the synthesis, Overman applied the Corey-Winter olefination, which addressed the problem Kende faced in a late stage dehydrative strategy. Reaction of the diastereomeric mixture of diols **2.43** with thiophosgene gave cyclic thiocarbonates **2.44** in a 68% yield as a mixture (3.5:1) of *syn*- and *anti*-diastereomers. Phosphite mediated olefination on each of the purified thiocarbonates gave targets **2.3** (66% yield from the corresponding *syn*-product) and **2.4** (64% yield from the *anti*-product). The total synthesis of didehydrostemofoline (**2.3**) was accomplished in 33 step total steps and in roughly 0.2% overall yield.

2.1.2.3 Thomas - Partial Synthesis

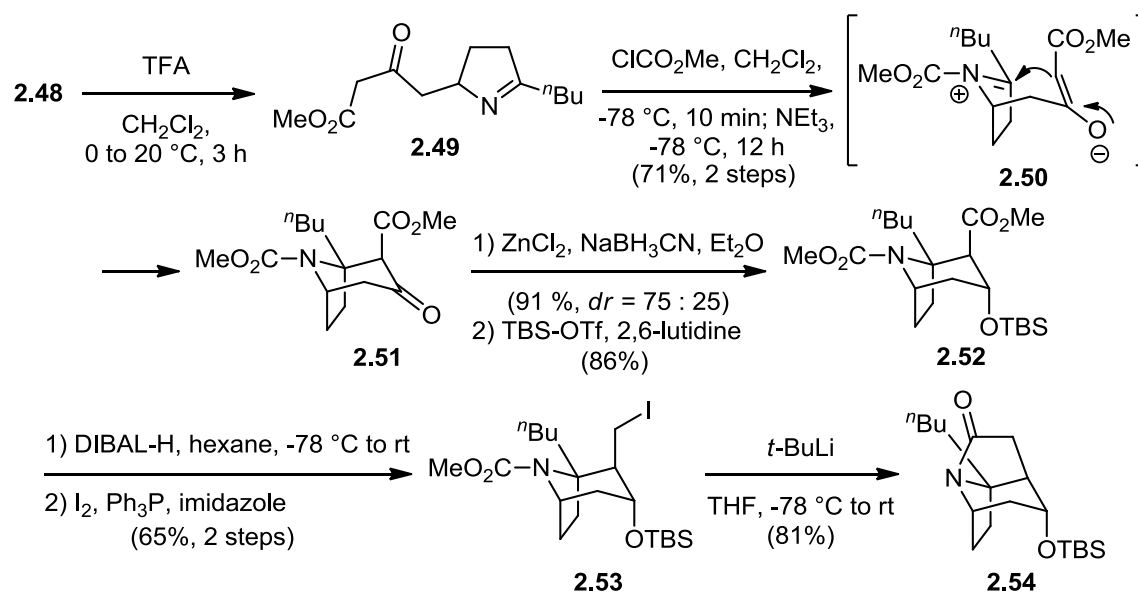
In 1992 a synthetic approach to the stemofoline core was reported by Thomas that utilized an intramolecular Mannich reaction to assemble an initial bridged azabicyclic scaffold, which served as a platform for construction of the tricyclic core. This initial account has since been followed by two subsequent publications, one of which reported significant progress toward applying the following chemistry on enantioenriched substrates.⁷⁵⁻⁷⁷ The synthetic effort commenced by protecting the nitrogen of lactam **2.45** as its *t*-butyl carbamate, followed by the addition of *n*-butyl magnesium bromide into the imide carbonyl to give ketone **2.46** in 69% yield over the two step sequence (Scheme 2.8). Ketone **2.46** was then protected as an acetal and the terminal olefin was subjected to ozonolysis to provide aldehyde **2.47** in 73% yield (2 steps). The addition of the enolate of methyl acetate, followed by oxidation of the resulting aldol product gave β -ketoester **2.48** in 69% from aldehyde **2.47**.

Scheme 2.8



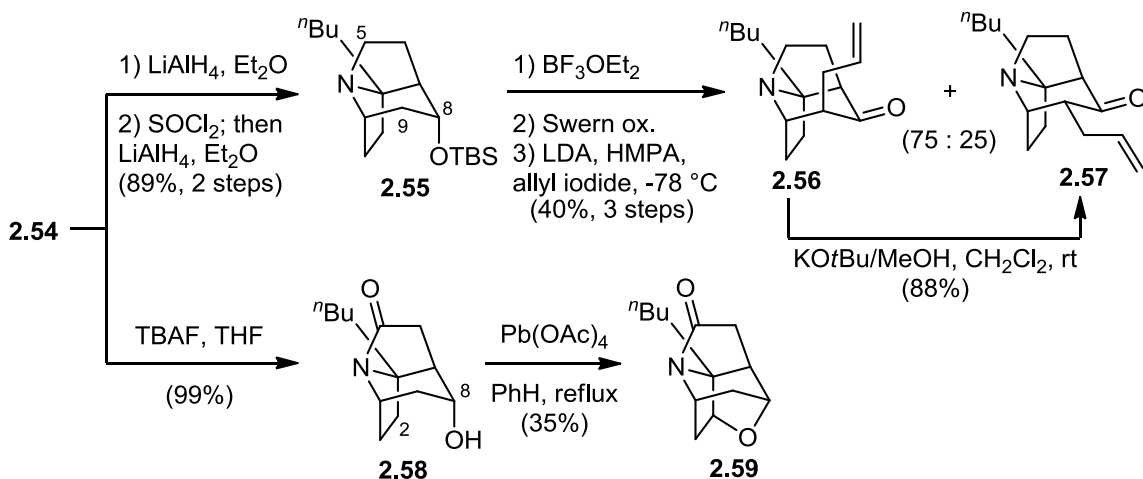
β -ketoester **2.48** provided the carbon and functional framework necessary to elaborate into the tricyclic core of stemofoline. As such, the removal of the Boc-protecting group with TFA unmasked the amine, which condensed spontaneously with the attached ketone to give the pyrroline **2.49** (Scheme 2.9). The crude imine was then treated with methyl chloroformate to give a putative acyl iminium ion, which underwent an intramolecular Mannich with the β -ketoester moiety upon treatment with Et_3N . Azabicycle **2.51** was thus furnished in 71% yield over the two step sequence.

Scheme 2.9



With the azabicycle **2.51** in hand, the ketone was reduced with zinc cyanoborohydride to give a mixture (75:25) of the axial and equatorial alcohols (Scheme 2.9). The axial alcohol was then protected as its *t*-butyldimethylsilyl ether to give **2.52** in 58% yield over the two steps. Reduction of the ester **2.52** to the corresponding alcohol with DIBAL-H and iodination delivered alkyl iodide **2.53** in 65% yield (2 steps). Lithium-halogen exchange of the iodide **2.53** with *t*-BuLi then gave an organolithium intermediate, which underwent intramolecular acylation with the carbamate moiety to give the azatricycle **2.54** in 81% yield. With this compound in hand, a few different concepts were tested for functionalizing the tricyclic core of stemofoline.

Scheme 2.10



While lactam **2.54** contained the requisite carbon framework of stemofoline, additional experiments were performed to establish the viability of **2.54** with respect to a total synthesis (Scheme 2.10). The superfluous lactam functionality was first removed by reducing **2.54** with LiAlH_4 to provide the corresponding cyclic N,O-acetal. The lactam did not fully reduce to the amine as is typical with lactams, and thus an additional activation with thionyl chloride was required. The intermediate formed upon treatment with SOCl_2 was reduced in the same pot an additional treatment with LiAlH_4 to complete the reduction at C(5) providing amine **2.55** in 89% over the three step/two-pot sequence. The stability of the N,O-acetal intermediate and the presumed α -chloroamine, suggests that the bridged nitrogen is incapable of adopting an sp^2 -hybridized geometry, and thus the bridgehead nitrogen atom cannot contribute to the expulsion of the α -leaving group. The α -chloroamine that is formed upon treatment with SOCl_2 therefore behaves more like an alkyl chloride, which can be reduced to their corresponding alkanes by reduction with anionic hydride reagents. With the C(5)-position refunctionalized, the C(8)-silanol was oxidized to the C(8)-ketone by desilylation and oxidation under Swern conditions.

The C(9)-substitution was then installed via allylation of the corresponding enolate to give mostly the axially substituted ketone **2.56**. Thermodynamic equilibration of the axially substituted compound gave the more thermodynamically stable equatorially substituted compound **2.57** in 88% yield.

Lactam **2.54** was also used to test the concept of oxidizing the C(2)-position using a remote functionalization (Scheme 2.10). Deprotection of C(8)-silanol gave the alcohol **2.58**, which, upon treatment with lead tetracetate, gave an oxygen centered radical capable of extracting a hydrogen atom from the C(2)-carbon. The reformation of the oxygen radical facilitated a recombination reaction to functionalized the C(2)-position as the ether **2.59** in 35% yield. No functionalization of the C(3)-position was observed after the reaction; however, the starting material was recovered in 12% yield along with 16% of the oxidized C(8)-ketone product. While the remote functionalization of the C(2)-position in this way is noteworthy, it is not clear how this strategy will be adapted to achieve the higher acetal oxidation state at C(8)-position required for stemofoline.

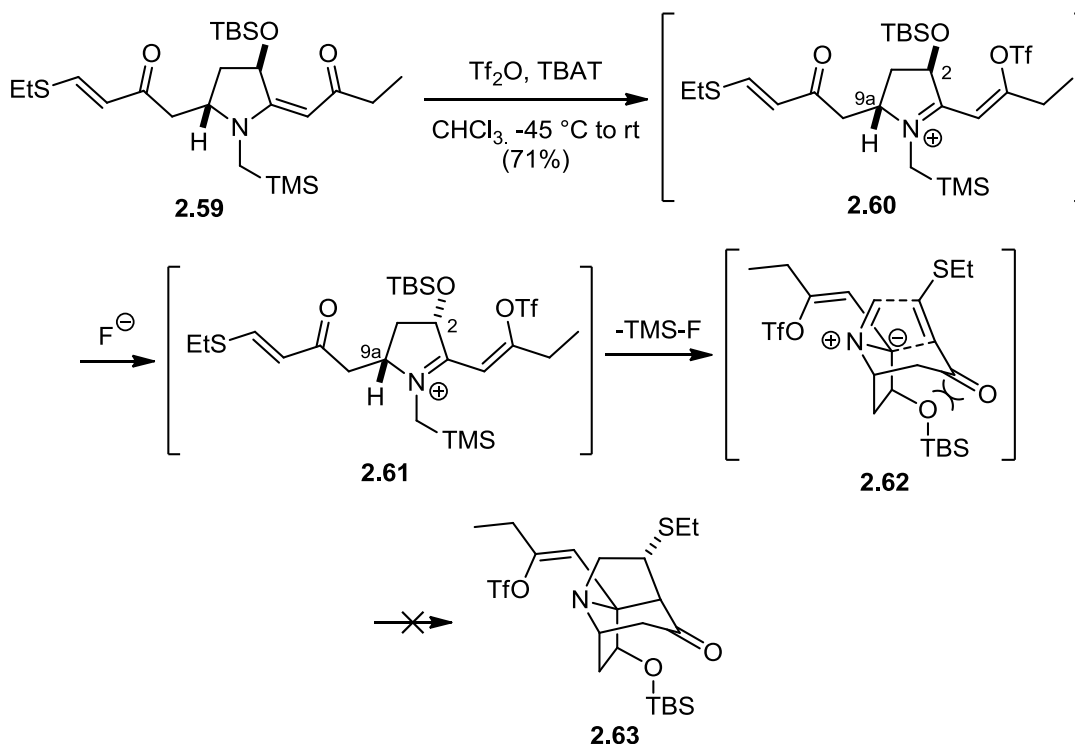
Efforts are still ongoing in the Thomas group to expand this general strategy into a total synthesis of stemofoline. Recent accounts from their group have demonstrated the efficacy of their approach to achieve an asymmetric synthesis; however, the preparation of the full tricyclic core has not yet been reported in that vein.

2.1.2.4 Gin - Partial Synthesis

The approach that was devised by Gin, first reported in 2002, focused on the construction of the stemofoline core via an intramolecular 1,3-dipolar cycloaddition of a azomethine ylide with an appended activated dipolarophile.^{14, 15} The initial cycloaddition substrate chosen was vinylogous amide **2.59**, which possessed the required C(2)-alcohol, albeit in the opposite stereochemical conformation required for stemofoline

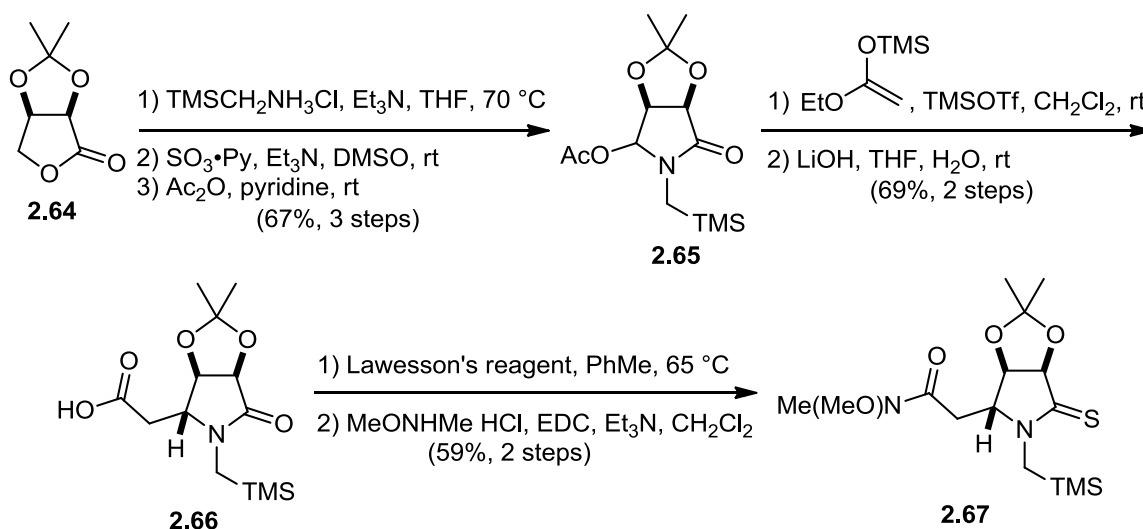
(Scheme 2.11). Attempting to form an azomethine ylide from this substrate by first treating with triflic anhydride presumably gave the vinylogous iminium ion **2.60**. Subsequent reaction of the iminium ion with *t*-butyl ammonium trifluorosilicate (TBAT), rather than generating the desired azomethine ylide, resulted first in a presumed epimerization of the C(2)-alcohol leading to iminium ion **2.61**. It was then postulated that the azomethine ylide **2.62**, resulting from desilylation of iminium **2.61**, was incapable of achieving the envisioned dipolar cycloaddition transition state **2.62** because of the severe steric interaction with the *endo*-silanol and the newly forming piperidine ring. This attempted cycloaddition was reported to give a complex mixture, and none of the desired cycloadduct **2.63** was observed.

Scheme 2.11



Due to the failure of their first approach, a second generation was devised, which targeted a cycloaddition substrate incapable of epimerization during the azomethine ylide formation (Scheme 2.12). Using *O*-isopropylidene-D-erythrone (2.64) as the starting material, a cycloaddition substrate could be accessed bearing a 5,5-*cis*-fused ring system. This modification would render the cycloaddition substrate incapable of epimerization during the cycloaddition since the product of epimerization would be a 5,5-*trans*-fused ring system, which is not possible. In order to test this hypothesis, 2.64 was first treated with (trimethylsilyl)methyl amine, and the resulting alcohol product was oxidized under Parikh-Doering conditions. The resulting hemiaminal was then acetylated to give 2.65 in 67% yield over the three step sequence. The aminor 2.65 was then treated with TMS-OTf and the silyl ketene acetal of ethyl acetate resulting in a Mannich reaction to install the acetate side chain, which was saponified to give carboxylic acid 2.66 in 69% overall yield. The lactam 2.66 was converted to its thiolactam with Lawesson's reagent, and the carboxylic acid was converted to Weinreb amide 2.67 in 59% yield over the two steps.

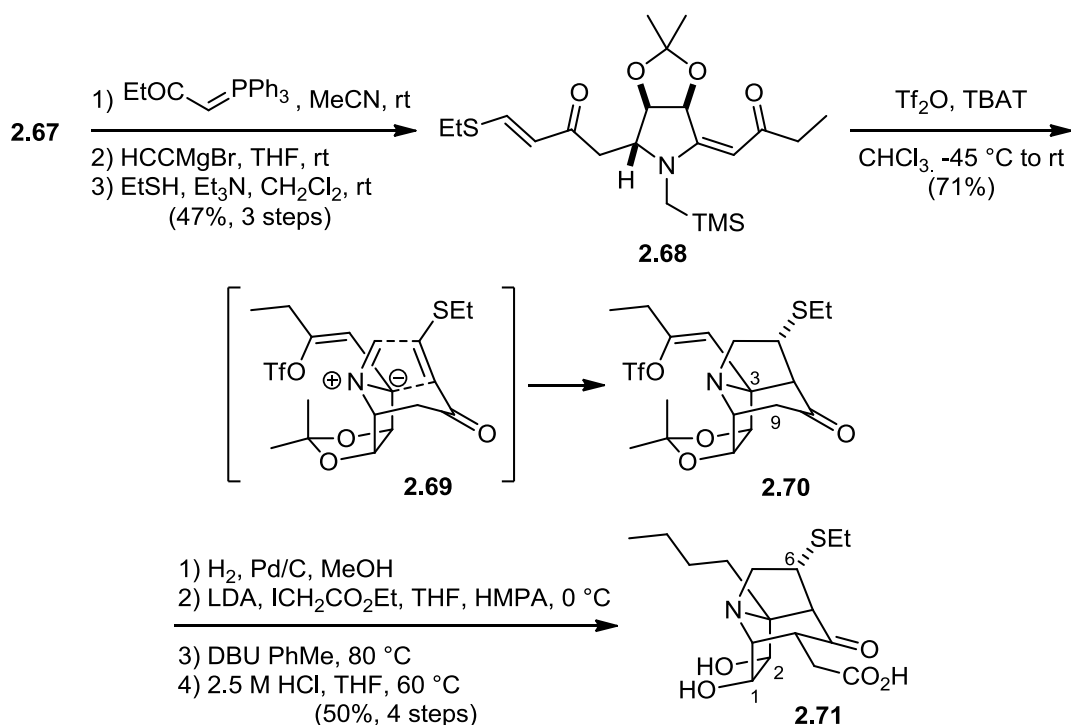
Scheme 2.12



With **2.67** in hand, the requisite functionality for the cycloaddition was swiftly installed (Scheme 2.13). Over a three step sequence, **2.67** was first olefinated to give a vinylogous amide under Wittig conditions. The dipolarophilic side chain was thus installed by addition of ethynyl Grignard reagent to give an ynone, which was activated as its vinylogous thioester by 1,4-addition of ethane thiol to give the cycloaddition precursor **2.68** in 47% overall yield. Treatment of **2.68** with triflic anhydride and TBAT resulted in an azomethine ylide that underwent the desired intramolecular cycloaddition via the intramolecular transition state **2.69** to give cycloadduct **2.70** in 71% yield. The tricyclic cycloadduct was then refunctionalized by first performing an exhaustive reduction of the C(3)-side chain. The C(9)-side chain was then installed following the Overman protocol. Finally, hydrolysis of the acetonide delivered diol **2.71** in 50% over the four step sequence. This tricycle bears the required functionality in the stemofoline core; however, the superfluous C(6)-thiol and the C(1)-alcohol must be removed from the molecule selectively in the presence of the C(2)-alcohol. Furthermore, the C(2)-

stereocenter would have to be inverted for it to be clear that **2.71** is a viable intermediate in a total synthesis of stemofoline.

Scheme 2.13



Despite the extra functionality in **2.71**, it is noteworthy that the tricyclic core of the stemofoline alkaloids bearing the appropriate C(3) and C(9)-side chains was accessed in an asymmetric form in 15 total steps.

2.1.2.5 Summary

The synthetic approaches discussed in this first section represent a number of excellent tactics to access the stemofoline core. The completed total syntheses, however, were rather long requiring >26 steps and provided low overall yields of the final natural product(s). Furthermore, neither of these total syntheses were performed asymmetrically

which represent an opportunity for further development. While Thomas has reported an asymmetric approach to the stemofoline core, the most advanced intermediate he has reported is not an intermediate which is clearly viable toward a total synthesis. The Thomas intermediate **2.71** bears two extraneous functional groups at the C(6) and C(1)-positions and inappropriate stereochemistry at the C(2)-carbon. Thus the challenge of a viable asymmetric synthesis of the stemofoline alkaloids is an unsolved problem.

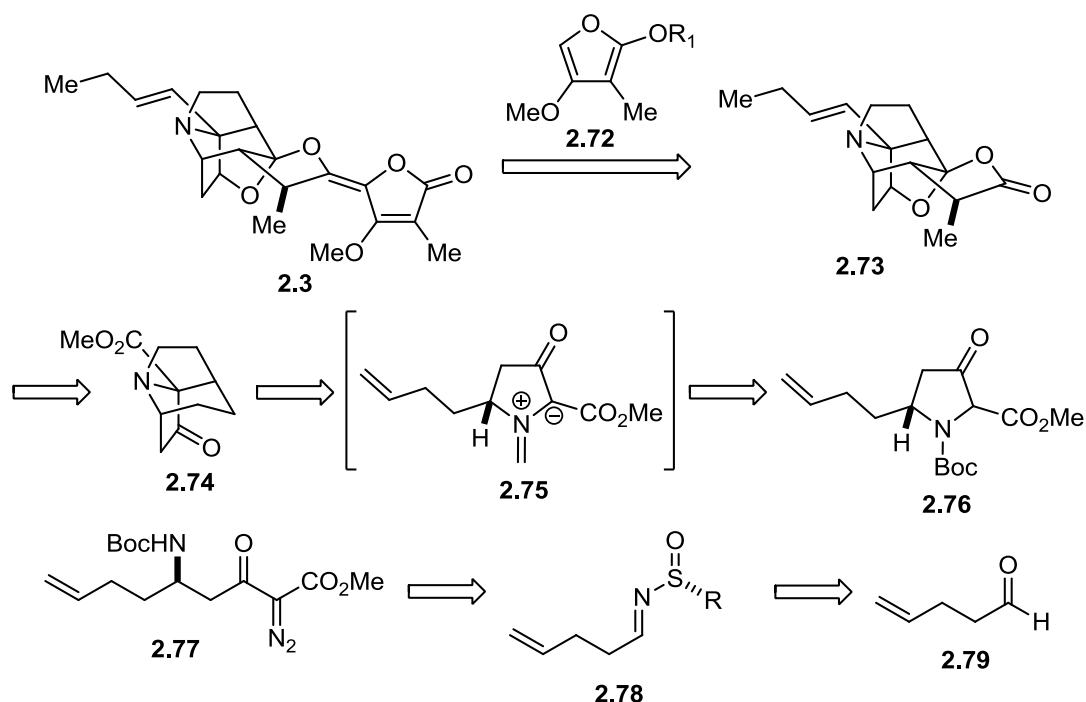
2.1.3 Prior Art in the Martin Group

2.1.3.1 Introduction/Early Studies

Synthetic studies toward the stemofoline natural products have been ongoing in the Martin Group for approximately ten years,^{39, 40, 79-82} and is part of our group's longstanding interest in the synthesis of the biologically and structural interesting family of *stemona* alkaloids.^{83, 84} While the proposed syntheses themselves have progress through a number of iterations, many of the critical disconnects have remained the same (Scheme 2.14). We have long targeted lactone **2.73** as an intermediate that we felt could be used to directly install the butenolide moiety. Kende reported that his group unsuccessfully attempted to elaborate a similar intermediate to stemofoline, but we felt that this intermediate still represents the most direct pathway to the stemofoline alkaloids. Although it may prove to be a considerable challenge, we felt that a coupling of either the lithium furanone anion or a siloxy furan of compound **2.72** with an oxonium ion generated from the reaction of **2.73** with Meerwein's salt (or via a similar activation mode) would provide a highly reactive electrophile for this coupling. The addition of the furanone nucleophile into the oxonium formed by reaction with Meerwein's salt would not be susceptible to the "retro-aldol" process that Kende described because the product

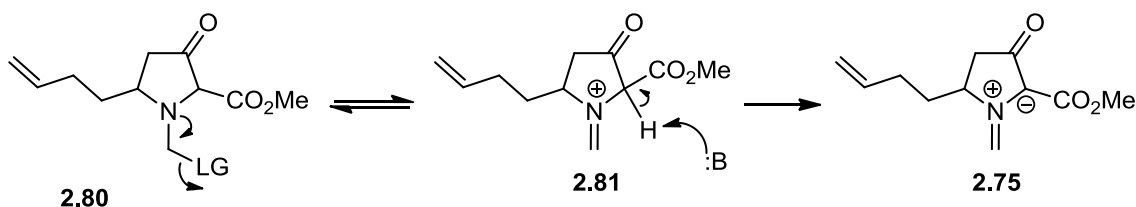
formed upon addition would not be a free oxygen, thus the reformation of carbonyl would not be possible. We envisioned that compound **2.73** would be ultimately obtained by a remote radical functionalization of the C(8)-position by an alcohol derived from ketone **2.74**. In this way we hoped to install an appropriate functional handle to install an appropriate C(9)-side chain. This concept was essentially proven by Thomas in the reverse sense (Scheme 2.10); however, we sought to adopt chemistry developed by either Suarez or Barton because their chemistry would allow for a direct double functionalization.⁸⁵⁻⁹⁰ The tricyclic compound **2.74** would then be obtained from an intramolecular 1,3-dipolar cycloaddition of an azomethine ylide **2.75** derived from pyrrolidinone **2.76**. The pyrrolidinone intermediate could be accessed using chemistry extensively developed by Davis,⁹¹⁻⁹⁶ whereby an intermolecular Mannich/cross-Claisen reaction of sulfoximine **2.78** would set the stage for a rhodium catalyzed intramolecular NH-insertion reaction of diazo compound **2.77**.

Scheme 2.14



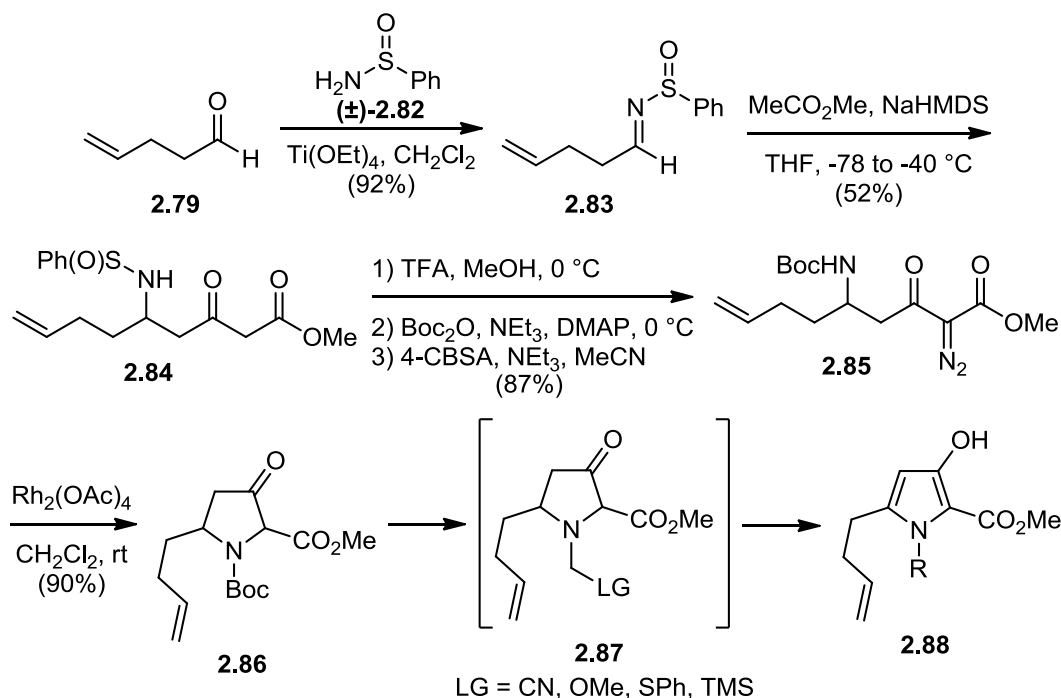
The most notable challenge in the proposed synthesis is the 1,3-dipolar cycloaddition, and this reaction accounts for the majority of the effort our group has invested in endeavors toward the total synthesis of these challenging alkaloids. We envisioned generating the targeted azomethine ylide by installing a leaving group alpha to the pyrrolidinone nitrogen atom so that expulsion of the leaving group would generate an iminium ion **2.81** (Scheme 2.15). Deprotonation of this iminium ion would give the polarized azomethine ylide **2.75**, which we hoped would then cyclize on the appended unactivated olefin to give the stemofoline core.

Scheme 2.15



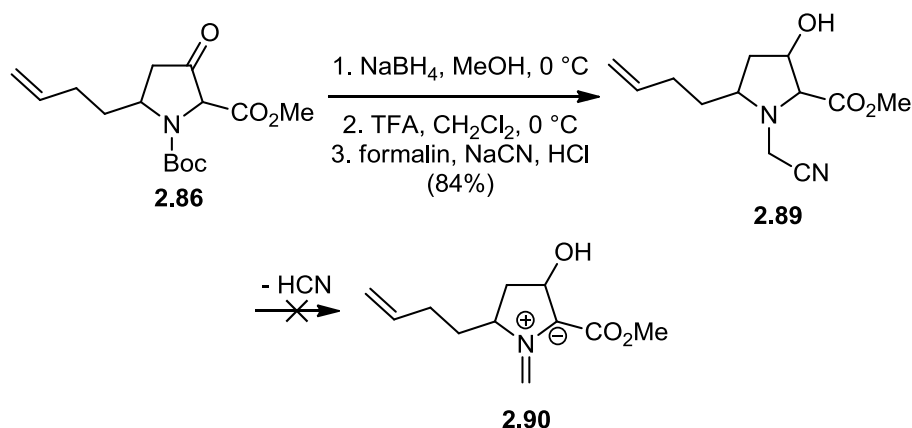
In order to test the feasibility of our plan, the simplest conceivable substrate for this cycloaddition was targeted using chemistry developed by Davis for the synthesis of 5-substituted pyrrolidinones (Scheme 2.16). The synthesis of **2.86** commenced with 4-pentenal (**2.79**), which was condensed with racemic sulfoxamide **2.82** to give sulfoximine **2.83** in 92% yield. A tandem Mannich/cross-Claisen reaction was performed with excess of the enolate of methyl acetate to give β -ketoester **2.84** in 52% yield. The impending NH-insertion reaction has been shown to be incompatible with the sulfoxamide moiety,^{97, 98} and thus the sulfoxide must first be removed and replaced with a carbamate; in this case the *t*-butyl carbamate was installed. A diazo transfer of β -ketoester **2.84** was then performed to give diazo- β -ketoester **2.85** in 87% yield over the three steps. Treatment of the diazo carbamate with catalytic rhodium acetate resulted in an NH-insertion reaction to provide pyrrolidinone **2.86**. At this point a number of different strategies were screened in order to remove the Boc-protecting group and replace it with a methylene subunit capable of providing the required azomethine ylide. These attempts, however, proved fruitless. For the most part, the only isolable products were the corresponding pyrroles **2.88**, either as the free pyrrole or the N-substituted variant. These products presumably form as a result of rapid oxidation of the amino pyrrolidinones that result from removal of the electron withdrawing carbamate protecting group.

Scheme 2.16



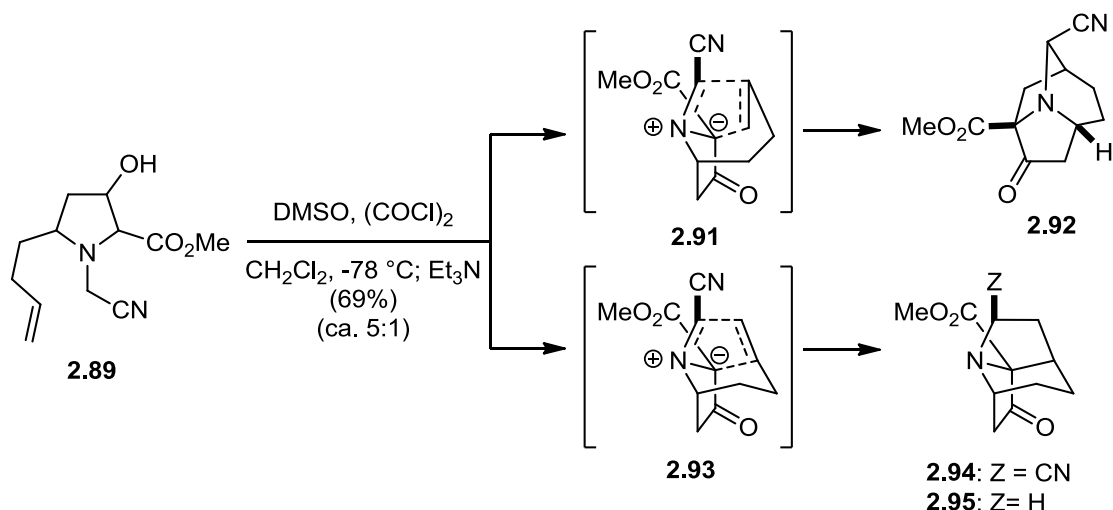
In order to access a substrate such as **2.87**, it was rationalized that the ketone would have to first be reduced to obviate the oxidation pathway (Scheme 2.17). Ketone **2.86** was thus reduced to give an inconsequential mixture of diastereomers, and the amino nitrile moiety was installed by removing the Boc-protecting group and subjecting the intermediate secondary amine to Strecker conditions. The amino nitrile **2.89** in this case was air stable; however, attempts to ionize **2.89** by expulsion of HCN were again unsuccessful.

Scheme 2.17



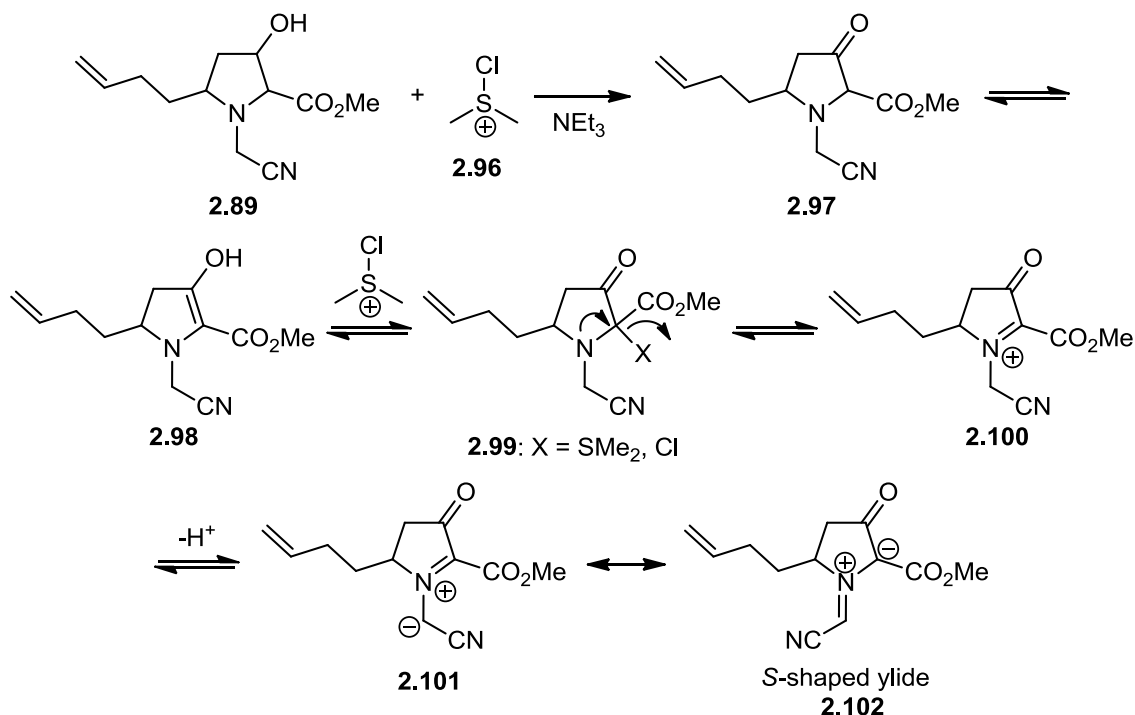
The first successful cycloaddition to construct the stemofoline core was accomplished serendipitously by Dr. Jochen Dietz (Scheme 2.18).⁸⁰ It was hoped that by oxidizing **2.89** to the β -ketoester under air-free conditions would result in the spontaneous generation of the originally targeted azomethine ylide. While attempting to oxidize alcohol **2.89** under Swern conditions, not only did the oxidation occur, but the ketone reacted further to give a cyanated-azomethine ylide **2.102**, which reacted via two regioisomeric transition states **2.91** and **2.93** to furnish a mixture (ca. 5:1) of cycloadducts **2.92** and **2.94** in 69% combined yield. The desired regioisomer **2.94** was obtained as the major product, but surprisingly the cyano “leaving group” was incorporated into the cycloadduct. The structure of **2.94** was determined using ^1H NMR, ^{13}C NMR, MS, and X-ray crystallography.

Scheme 2.18



With the cyano-group being maintained in this cycloaddition reaction (Scheme 2.18), it was clear that this particular cycloaddition was operating *via* an unprecedented type of reactivity. A proposed mechanism can be formulated to account for this observation (Scheme 2.19), whereby alcohol **2.89** first underwent a typical Swern oxidation to form ketone **2.97**. Compound **2.97** was then reacted with an additional equivalent of chlorodimethylsulfonium chloride (**2.96**) to install a leaving group alpha to the nitrogen atom, which might be either a dimethyl sulfonium group or a chloride. Subsequent elimination of the leaving group generated an iminium ion that was deprotonated to give the trisubstituted azomethine ylide **2.102**, bearing the *S*-shaped geometry with respect to the ester and cyano-groups. This ylide then underwent a facile 1,3-dipolar cycloaddition at -78 °C to give the product **2.94** with the cyano- and ester groups *anti* to one another. The *S*-shaped ylide geometry is presumed based on the confirmed stereochemistry of the cycloadduct; as discussed in the previous Chapter the ylide geometry relates directly to the observed stereochemistry of the pyrrolidine ring that is formed during the cycloaddition.

Scheme 2.19

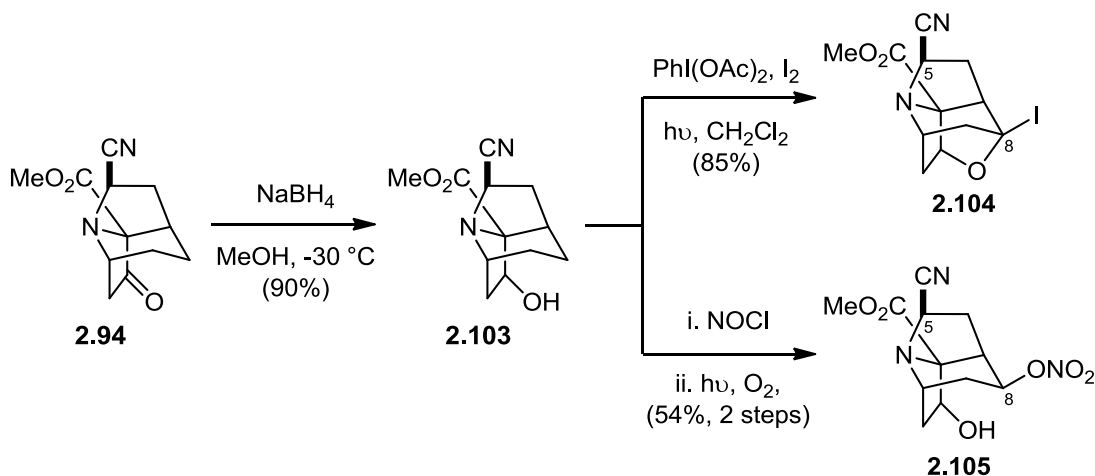


This initial cycloaddition provided important evidence that the proposed strategy to the stemofoline core was indeed possible; however, our inability to decyanate the tricycle **2.94** to give **2.59** under a variety of conditions obviated the use of this novel cycloaddition reaction for a total synthesis.^{39, 80} Due to the robust nature of the C(5)-cyano group, the search for an optimal set of cycloaddition conditions was continued in order to access a functional stemofoline core without the superfluous functionality.

It was of interest, however, to utilize the tricyclic molecule **2.94** to explore some of the proposed disconnects in our synthetic plan for the stemofoline alkaloids. Further efforts by Dr. Dietz proved the viability of a proposed remote radical functionalization at the C(8)-position of the natural product core (Scheme 2.20). In the event, a stereoselective reduction of ketone **2.94** set the critical C(2)-stereocenter so it could be

utilized as a handle to functionalize the C(8)-position. Employing two different sets of conditions developed by Barton and Suarez, the C(8)-center was functionalized to give either iodoether **2.104** or nitrate **2.105**. Unfortunately, further attempts to decyanate any of these intermediates were again not successful.

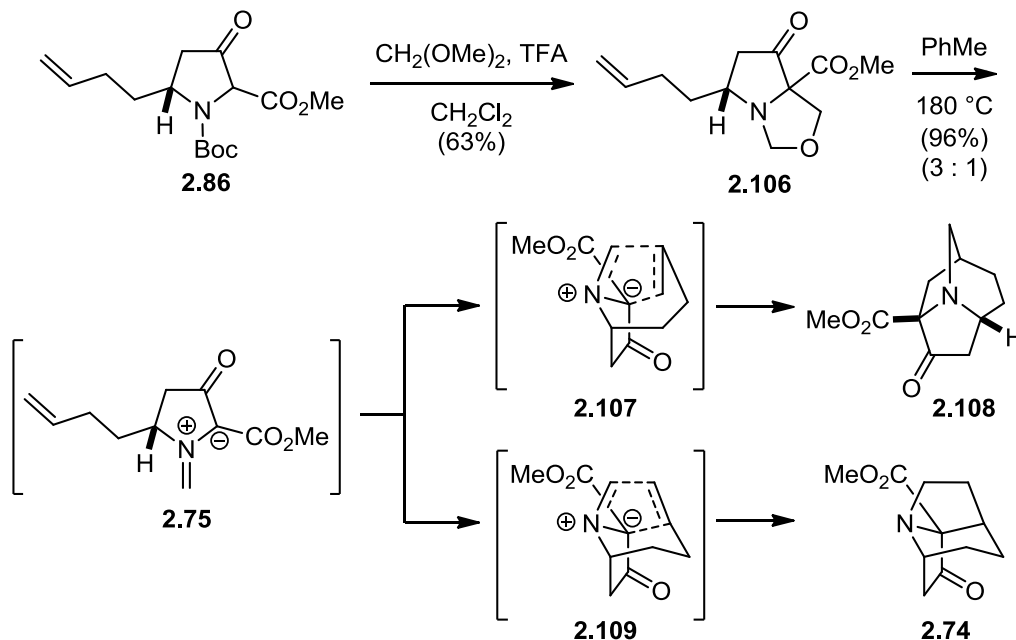
Scheme 2.20



In later work, Dr. Bjorn Ludolph was able to effect the key cycloaddition using a different set of cycloaddition conditions (Scheme 2.21).⁸¹ Based on work developed by Joucla, who showed that flash vacuum thermolysis (FVT) of oxazolidines generated azomethine ylides capable of both inter- and intramolecular cycloadditions,^{55, 56} we reasoned that a similar approach in our hands might facilitate the desired cycloaddition. Starting with Boc-protected pyrrolidinone **2.86**, oxazolidine **2.106** was accessed *via* a one-pot procedure by treatment with TFA in the presence of dimethoxymethane. Heating oxazolidine **2.106** in a sealed tube at $180\text{ }^\circ\text{C}$ resulted in a retro-cyclization (liberating formaldehyde) to give an azomethine ylide, which reacted through two regioisomeric transition states **2.107** and **2.109** to give a mixture (1:3) of cycloadducts **2.108** and **2.74** in 96% yield. While this reaction provided a good yield of the cycloaddition products, the

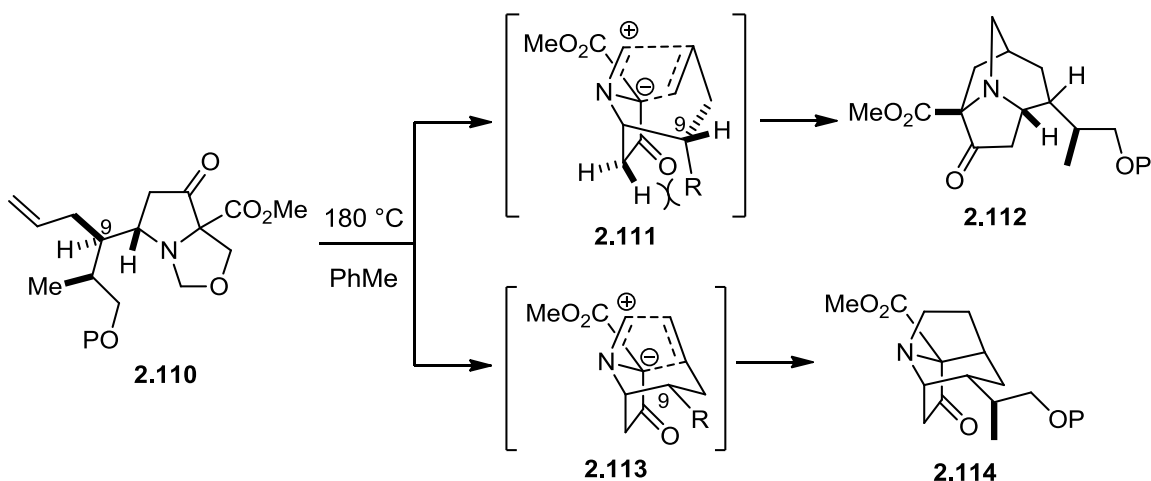
undesired cycloadduct was significantly favored in the reaction. This precedent, however, provided a good starting point for the potential application of similar oxazolidines in future studies.

Scheme 2.21



In order to improve the ratio of products to favor the desired tricycle, it was rationalized that a destabilizing steric interaction could be introduced in the undesired transition state **2.111** *en route* to the undesired tricycle **2.112** (Scheme 2.22). We reasoned that by incorporating a bulky substituent at the C(9)-position of the dipolarophilic side chain of oxazolidine **2.110**, which mapped on to an advanced intermediate in a potential synthesis of the stemofoline alkaloids such as **2.114**, that the increased steric hindrance would steer the cycloaddition toward the desired regioisomer by disfavoring the undesired transition state **2.113**. To test this hypothesis, a new synthetic plan was devised to address the synthesis of this considerably more complex system.

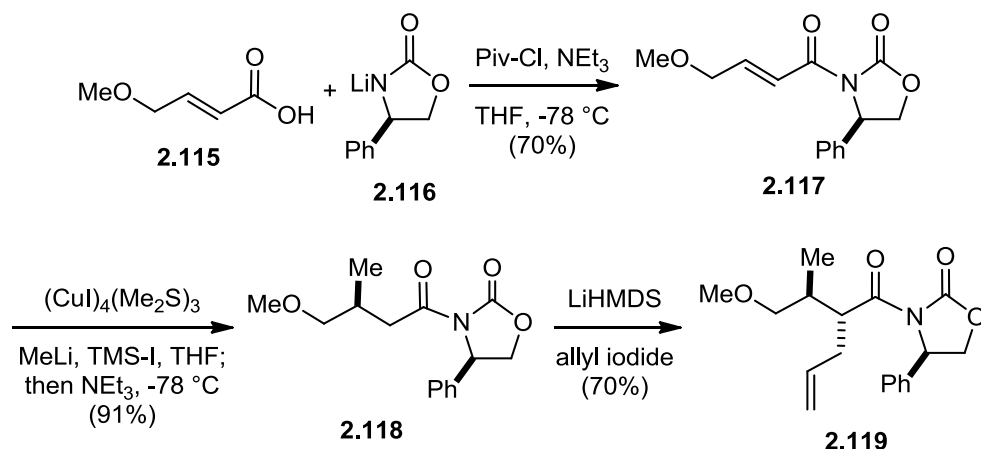
Scheme 2.22



2.1.3.2 Approach to a Sterically Biased Cycloaddition Substrate

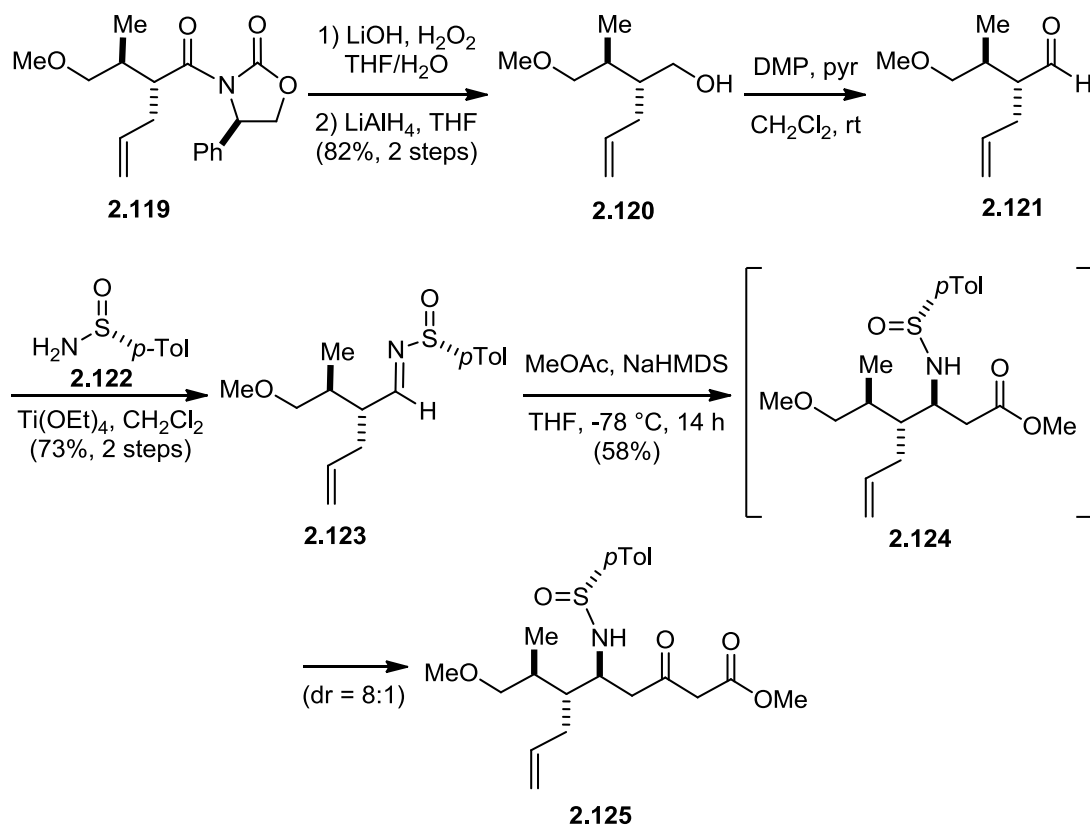
The synthesis of a derivative of **2.110** that incorporated the C(9)-side chain in the targeted azomethine ylide was the focus of work by Dr. Nathan Fuller,⁸² who built upon preliminary studies by Dr. Bjoern Ludolph.⁸¹ The effort commenced with coupling the mixed anhydride derived from commercially available carboxylic acid **2.115** and the lithium anion of the D-phenylglycine derived Evan's chiral auxiliary **2.116** to provide the α,β -unsaturated imide **2.117** in 87% yield (Scheme 2.23). Conditions developed by Hruby⁹⁹ and Bergdahl¹⁰⁰ were used to install the desired methyl group *via* conjugate addition of dimethyl cuprate into **2.117** giving a mixture (7:1) of diastereomers favoring **2.118** in 91% isolated yield. The absolute stereochemistry of **2.118** was confirmed by X-ray crystallography. A subsequent alkylation using allyl iodide gave the disubstituted imide **2.119** in 70% yield.

Scheme 2.23



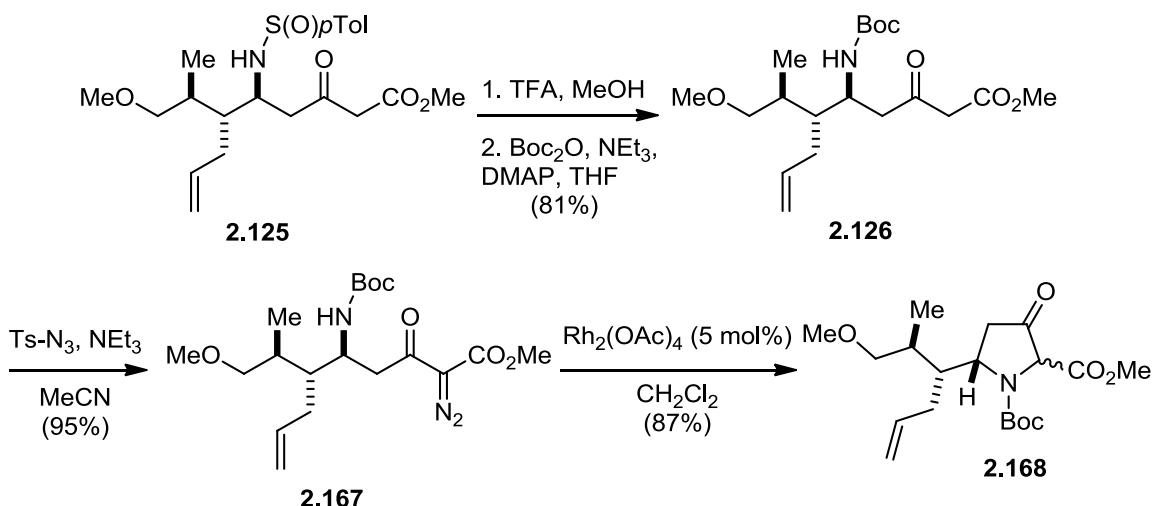
With the requisite stereocenters of the eventual C(9)-side chain installed, a number of steps were required to elaborate **2.119** into the pyrrolidinone cycloaddition precursor (Scheme 2.24). Removal of the chiral auxiliary from **2.119** was accomplished by the action of basic hydrogen peroxide followed by reduction of the resulting carboxylic acid with lithium aluminum hydride to provide alcohol **2.120** in 82% yield over two steps. The hydrolysis step also provided an 86% recovery of the chiral auxiliary (protio-**2.116**), which was recycled for future use. Oxidation of alcohol **2.120** with Dess-Martin periodinane provided aldehyde **2.121**. At this point the second chiral auxiliary was installed by reacting sulfoxamide **2.122** with aldehyde **2.121** *via* a titanium mediated condensation reaction to give sulfoximine **2.123** in 73% yield over the two step sequence. Sulfoximine **2.123** was then subjected to a tandem Mannich/cross-Claisen reaction with excess sodium enolate of methyl acetate to provide the desired β -ketoester **2.125** in 58% yield, however, this reaction was difficult to reproduce.

Scheme 2.24



The sulfoxide of **2.125** was next removed, and the resulting amine refunctionalized with a Boc-protecting group providing carbamate **2.126** in 81% yield over two steps (Scheme 2.25). Diazo transfer with tosyl azide (Ts-N_3) provided diazo compound **2.167** in 95% yield, and a subsequent rhodium catalyzed NH- insertion provided pyrrolidinone **2.168** in 87% yield as a mixture (1:1) of diastereomers.

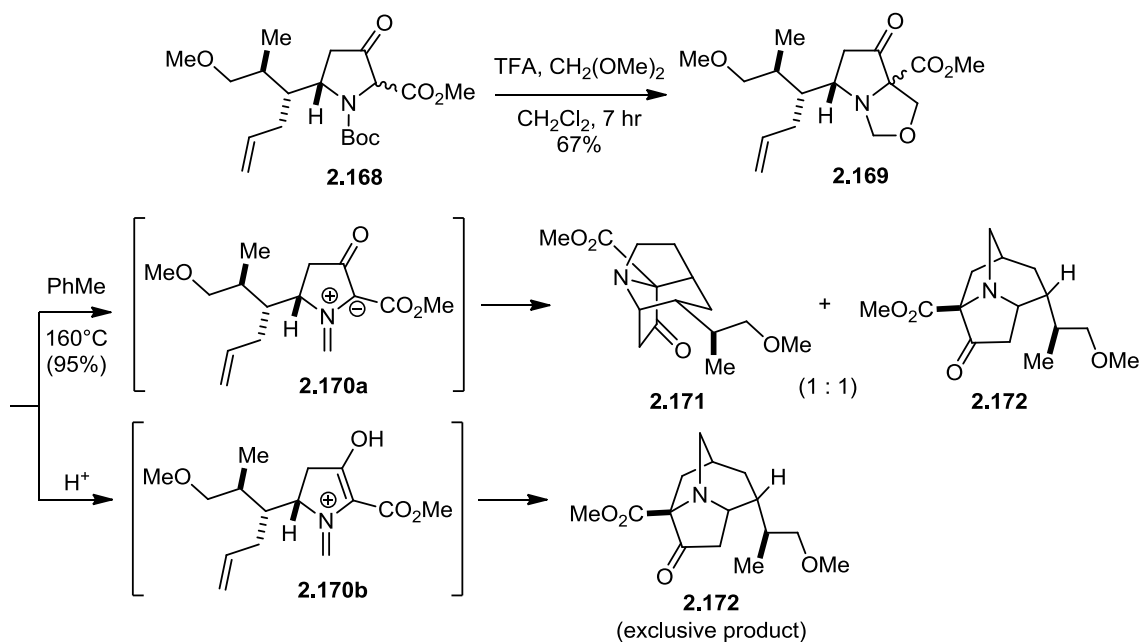
Scheme 2.25



With a synthetic route to compound **2.168** developed, the stage was set to examine the pivotal cycloaddition (Scheme 2.26). Pyrrolidinone **2.168** was first elaborated into the corresponding azomethine ylide precursor by removal of the Boc-group and concomitant heterocycle formation using excess TFA and dimethoxymethane to give oxazolidine **2.169** in 67% yield, a reaction that was invariably accompanied by the formation of the undesired cycloadduct **2.172**. The undesired cycloadduct forms presumably from the generation of an azomethine ylide by acid catalyzed decomposition of the oxazolidine, which gives enol iminium ion **2.170b**. A reaction time of 7 h was critical to obtain good yields of this reaction, because longer reaction times resulted in increasing amounts of the undesired cycloadduct. By subjecting **2.169** to thermolysis, the azomethine ylide **2.170a** was formed and reacted to give a mixture (1:1) of desired and undesired cycloadducts **2.171** and **2.172** was obtained in a 95% yield. It is interesting to note that attempts to improved the regioisomeric ratio of the cycloaddition never gave an increase over the 1:1 ratio, and under acidic conditions the only observable cycloadduct is the undesired **2.172**. While the reason for the inversion of selectivity is not clear, it

might be that the enol form of the azomethine ylide **2.170b** is capable of undergoing cyclization, but just not in the desired sense. This thermolysis result under neutral conditions, however, compared to the previous substrate where a mixture (1:3) of desired to undesired cycloadducts was obtained (Scheme 2.21), clearly validates the hypothesis that steric effects can be exploited to favorably affect the population of each of the regioisomeric transition states during the cycloaddition reaction. For the purposes of a total synthesis, however, we still felt that this increased selectivity still fell short of what we considered to be optimal. Many attempts were made by Dr. Fuller to further improve upon this ratio, including varying the temperature, pH, and solvent, however, a 1:1 ratio remains the most favorable selectivity to date. Performing the oxazolidine decomposition reaction under acidic conditions resulted exclusively in formation of the undesired cycloadduct. This result is hard to rationalize but does seem to suggest that the cycloaddition reaction under acidic conditions might be mechanistically different than under neutral pH. Despite the suboptimal selectivity in the cycloaddition of **2.169**, does provide an encouraging result from which to build upon. Subsequent work on the key step aimed to capitalize on this effect, however we were interested in investigating different structural modifications of the cycloaddition substrate to further enhance the selectivity. It is noteworthy, however, that a fully functionalized advanced core structure of the stemofoline alkaloids was accessed in asymmetric fashion in 14 total steps.

Scheme 2.26



2.1.3.3 Summary

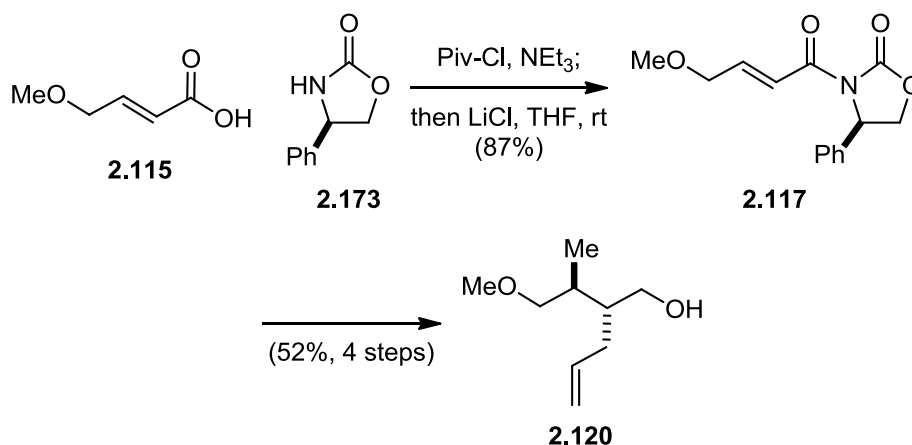
At this point in our efforts, we were able to access the appropriately functionalized core of the stemofoline alkaloids bearing the C(9)-side chain with the C(10)-methyl stereocenter. The synthesis of **2.168**, however, was difficult to perform on large scale, and when combined with the lower than desired selectivity of the key cycloaddition step, we were having difficulties pushing significant amounts of material past the desired cycloadduct **2.171**. We felt that an a fully optimized route to **2.168** might help in, not only furnishing more advanced material, but in allowing us to further explore modifications to the cycloaddition reaction in the hopes of discovering procedural elements that might lead to higher regioisomeric ratios. With the cycloaddition result to provide **2.171** in hand, we turned our attention to optimizing the steps leading up to the key cycloaddition step.

2.2 RESULTS & DISCUSSION

2.2.1 Further Progress on the C(9)-Substituted Cycloaddition Substrate

The Martin group cycloaddition strategy had thus evolved through a number of iterations as our understanding of the operative control elements of this key reaction continued to develop. For example, we had discovered that the method used to generate the azomethine ylide had a profound effect on the regiochemistry of the cycloaddition and that steric influences could be used to favorably tune the key step. What was missing at this point was a reliable and scalable synthesis which could provide useful quantities of advanced material. My own role on this project began with an effort to optimize the synthesis of the C(9)-substituted cycloaddition substrate to maximize the group's ability to advance the total synthesis via this cycloaddition reaction. Along these lines, the first synthetic improvement that was made was applying the Mathre procedure for installing the chiral auxiliary,¹⁰¹ whereby addition of LiCl to a mixture of the oxizolidinone **2.173** and the mixed anhydride of the carboxylic acid **2.115** facilitated a smooth coupling of these two fragments (Scheme 2.27). Previously, we had been using *n*-BuLi to pre-form the anion of **2.173**, but this procedure was difficult due to moisture sensitivity and the insolubility of the lithium anion. Furthermore, the yield was improved to 87% over the previously established 70% average. The steps used to advance **2.117** to **2.120** (*vide supra*) were not be improved through my work, however, this sequence remained one of the more difficult to scale up due to two consecutive steps which were air/moisture sensitive and provided mixtures of diastereomers. In order to obtain **2.120** in diastereomerically pure form from **2.117**, difficult chromatographic separations were required, which are only exacerbated on larger scales. This four step sequence, however, did manage to provide **2.120** in 52% yield.

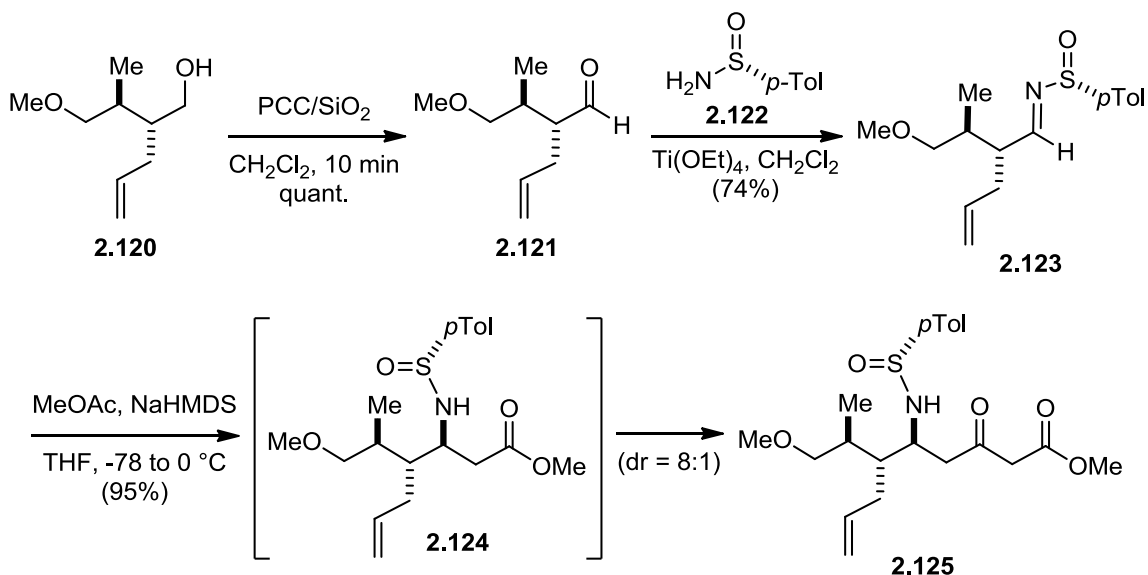
Scheme 2.27



Further improvements in the overall synthetic approach for this series of substrates came first from the oxidation of the alcohol **2.120** (Scheme 2.28). While the use of Dess-Martin periodinane was not necessarily problematic from the perspective of reaction yield, it is an expensive oxidant on large scale. The use of PCC as well as a Swern oxidation resulted in some epimerization of the alpha stereocenter; however, the combination of PCC/SiO₂ worked very well on large scale and, since the reaction was complete within 10 min, no epimerization was observed. This set of conditions also provided the analytically pure aldehyde **2.121** after filtration through a plug of silica gel. Condensation of aldehyde **2.121** with the chiral sulfoxamide **2.122** provided sulfoximine **2.123** in 74% yield as before. An additional improvement came from an extensive study of the tandem Mannich/cross-Claisen reaction on sulfoximine **2.123**. This step in the past never provided yields above 58% for the desired β -ketoester, and a great deal of the Mannich product **2.124** was always isolated that had not undergone the Claisen reaction. This ester **2.124**, despite being resubjected to the reaction conditions at -78 °C, could never be efficiently converted to the targeted β -ketoester. It was discovered, however, that warming the reaction to 0 °C resulted in efficient conversion of **2.124** to **2.125**. Since

the cross-Claisen step involves the addition of an enolate into the sulfoxamide anion, temperatures below -20 °C apparently could not provide the reaction with enough energy to form the required dianionic intermediate. Furthermore, when forming simple ester enolates the reaction is always accompanied by variable amounts of homo-Claisen reaction resulting in the formation of methyl acetoacetate as a byproduct. For our purposes, the lowering of the effective concentration of the enolate prior to introduction of the sulfoximine substrate was a troublesome variable to control and thus a large excess of methyl acetate and base was required (typically >10 eq). The optimization of this reaction has since proved useful for other Claisen reactions on substrates of this type.

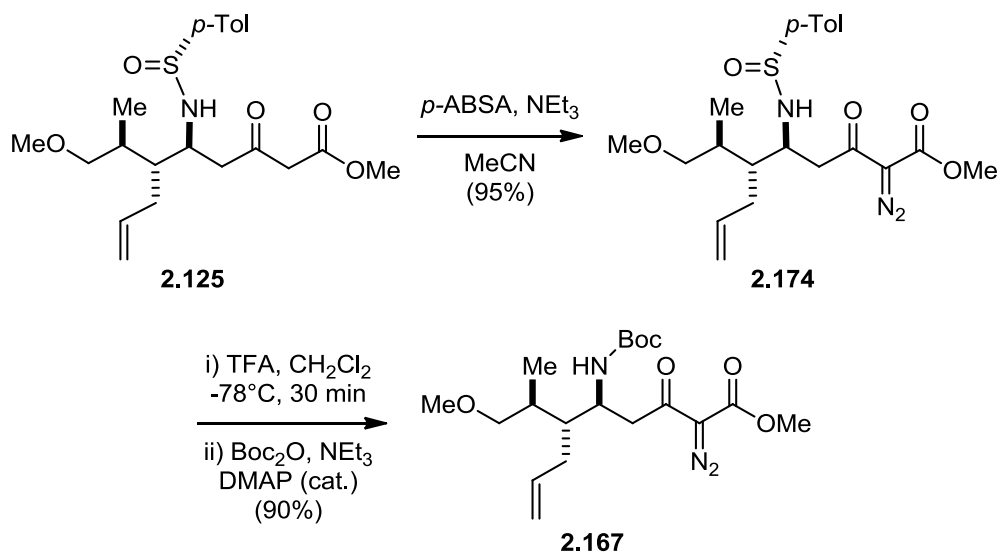
Scheme 2.28



An additional practical improvement to the overall sequence involved changing the diazo transfer agent from tosyl azide to *p*-acetamidobenzenesulfonyl azide (*p*-ABSA),¹⁰² which provided comparable yields of **2.174** to the corresponding carbamate analogue (Scheme 2.29). The *p*-ABSA reagent, however, is a more practically useful

reagent for synthesis due to the insolubility of the sulfonamide byproduct, which can be almost completely removed after the reaction via a precipitation and filtration. The tosyl azide byproduct (*p*-tolylsulfonamide) is much more soluble and requires a careful column to separate from the diazo product. One additional avenue that was investigated was inverting the order of the diazo transfer and reprotection steps. Previously the protecting group was changed to a Boc-group prior to the diazo transfer; however, when these steps were reversed, the overall yield of the process to access **2.2.167** improved to 86% overall yield from **2.174**.

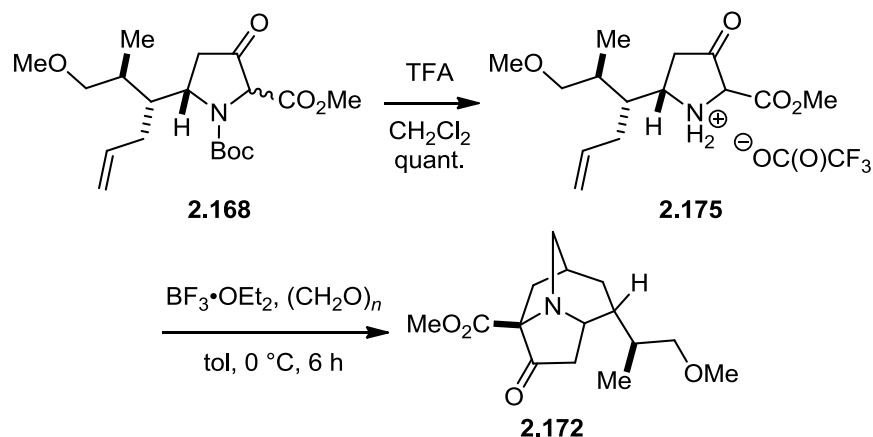
Scheme 2.29



With an improved synthesis to the cycloaddition precursor **2.168**, additional material was available and allowed for a brief study of the cycloaddition conditions; however, as mentioned earlier, any modification of the cycloaddition reaction that was made never resulted in an improvement of the already established 1:1 ratio. One specific attempt that successfully resulted in a cycloaddition reaction was to lower the reaction

temperature (from the usual 150 °C and above) by using $\text{BF}_3 \cdot \text{OEt}_2$ as a reagent to depolymerize paraformaldehyde and catalyze the formation of the desired azomethine ylide at 0 °C (Scheme 2.30). In this case, however, only the undesired cycloadduct was observed in the reaction. In another attempt to lower the thermolysis reaction temperature, the reaction was held at 100 °C for >5 days, but resulted in incomplete conversion and the regioisomeric ratio remained 1:1. Some variations in solvent were also investigated, but did not have an effect on the regioisomeric ratio.

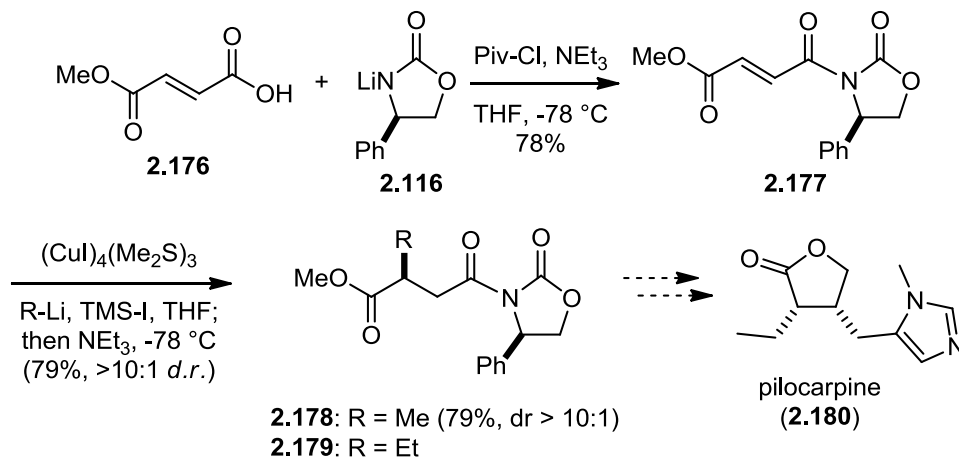
Scheme 2.30



The methyl ether moiety in the desired cycloadduct **2.171** was to eventually be utilized to access a carboxylic acid (or derivative thereof); but we were interested in the possibility of accessing the higher oxidation state at an early stage in the synthesis (Scheme 2.31). We rationalized that this change would, not only provide a more advanced cycloadduct, but might also add extra bulk to the C(9)-side chain and possibly enhance the regioisomeric ratio of the eventual cycloaddition. As part of our efforts to implement this plan, a novel method for the functionalization of desymmetrized fumarates such as imide **2.177** was discovered (Scheme 2.35). By subjecting fumarate

derivative **2.177** to the Hruby/Bergdahl conjugate addition conditions^{99, 100} we were able to directly access succinate **2.178** in good yield and high diastereoselectivity.

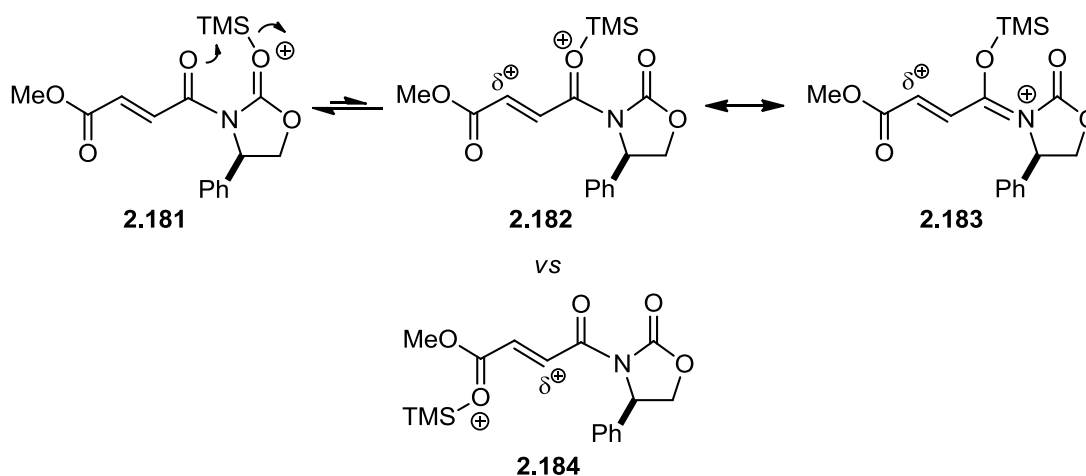
Scheme 2.31



The most notable aspect of this reaction was the remarkable regioselectivity, where virtually none of the undesired conjugate addition product was observed (Scheme 2.31). This observation can most likely be rationalized by comparing the reactivity of the carbonyl groups activating the olefin. An imide carbonyl group is more similar in electrophilicity to that of a ketone, making this the more reactive carbonyl compared to the ester carbonyl group. It therefore stands to reason that the imide carbonyl being the more reactive carbonyl group might have a correspondingly more reactive β -position. It is also important to consider the relative Lewis basicity of these carbonyl groups (Scheme 2.32). In the case of our conjugate addition example, TMS-I was used as the Lewis acid. If the Lewis acid/base adduct forms prior to addition of the nucleophile two adducts **2.182** and **2.184** are conceivable, which would be active to conjugate addition. The imide adduct **2.182** has one additional resonance structure compared to the ester adduct **2.184** that can contribute to stabilizing the oxonium intermediate, and thus the imide carbonyl is

the more basic. It is also possible though that an initial reaction of TMS-I with the most basic urethane carbonyl giving **2.181** that would selectively deliver the TMS-group to the neighboring imide carbonyl, thus facilitating the observed conjugate addition. Succinate **2.178** was a potentially useful intermediate for a total synthesis (Scheme 2.31); however, a subsequent refocusing of the stemofoline project diverted our attention to more fruitful areas. Despite the fact that **2.178** was not investigated further for a stemofoline synthesis we felt that this reaction was noteworthy in that it exhibited unprecedented reactivity to provide a potentially useful chiral succinate. Thus this reaction presents an opportunity for further development for accessing densely functionalized succinic acid and γ -butyrolactone derivatives. With these possibilities in mind, this method is currently under investigation in our group as a way to access important natural products targets such as the medicinally relevant pilocarpine (**2.180**) (via succinate **2.179**).¹⁰³

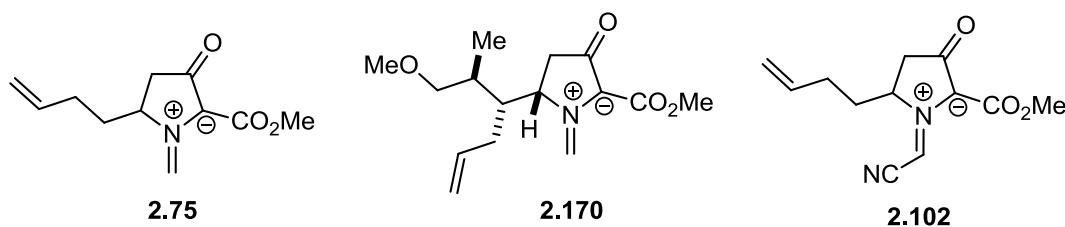
Scheme 2.32



At this stage, we became convinced that the approach of biasing the cycloaddition with only the C(9)-side chain was not going to a sufficiently selective approach to the stemofoline core. Not only did the key step provide no more than a 50% yield of the

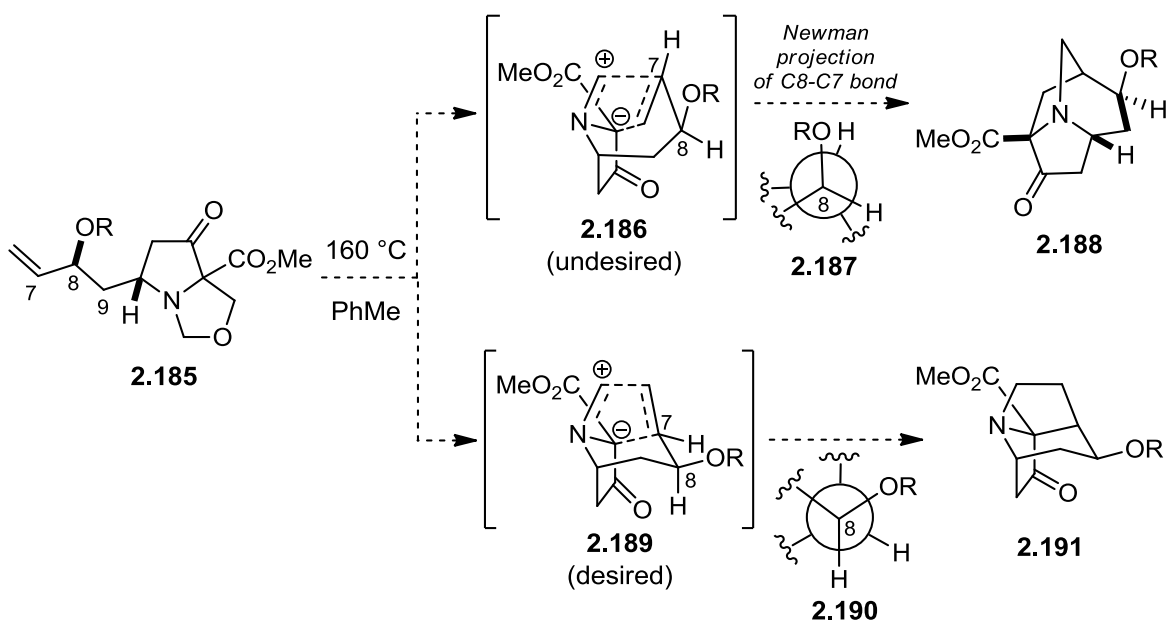
desired product, but the route was difficult to perform on the large scale needed to advance material. Furthermore, the approach we had adopted required the use of two different stoichiometric chiral auxiliaries, which we felt was not economical especially in light of the procedural limitations. The results with the dipolar cycloaddition, however, encouraged us to remain confident that the strategy would ultimately succumb to optimization and be made synthetically viable. To this point, we had only found two different methods that worked for generating an appropriate azomethine ylide (Scheme 2.33). The first of which was the Swern reaction that led to the formation of azomethine ylide **2.102**, which underwent a dipolar cycloaddition to give the natural product core at $-78\text{ }^{\circ}\text{C}$ with high regioselectivity. The reactivity of this azomethine ylide is most interesting in that there was no clear steric interaction that could be used to explain the high regioselectivity. It is clear, however, that the ylide **2.102** is considerably less polarized than the others, which suggested to us at the time that there was an electronic benefit in having an electron withdrawing group on the termini of the azomethine ylide. The second successful method we developed was the oxazolidine thermolysis reaction, which was used to access ylides **2.75** and **2.170**. This method allowed us to probe the efficacy of biasing the cycloaddition using steric effects, but, the manifestation of sterics in **2.170** was nowhere near as dramatic as the electronically biased example **2.102**.

Scheme 2.33



At this point we turned our attention to introducing substitution at the eventual C(8)-position of a cycloaddition substrate such as **2.185** based on the assumption that the steric interactions with this substituent would be more severe than the C(9)-substituent of **2.185** proved to be (Scheme 2.34). We were hopeful that the C(8)-substituent of **2.185** would prove more effective in guiding the thermolytic cycloaddition because of what we observed in transition state models when looking at the Newman projections about the C(8)/C(7)-bonds (such as **2.187** and **2.190**, Scheme 2.34). The undesired transition state appeared to have unfavorable eclipsing interactions, while the desired transition state on the other hand put the C(8)-hydroxyl group in the equatorial position of the newly forming chair-like ring. Targeting a cycloaddition substrate such as **2.185**, we felt would also provide a functional handle for completing the functionalization of the C(8) and C(9) positions of the stemofoline core. We also aimed to develop a more innovative synthetic strategy to access the cycloaddition precursor, which would prove more novel and effective at providing us with larger quantities of this material.

Scheme 2.34



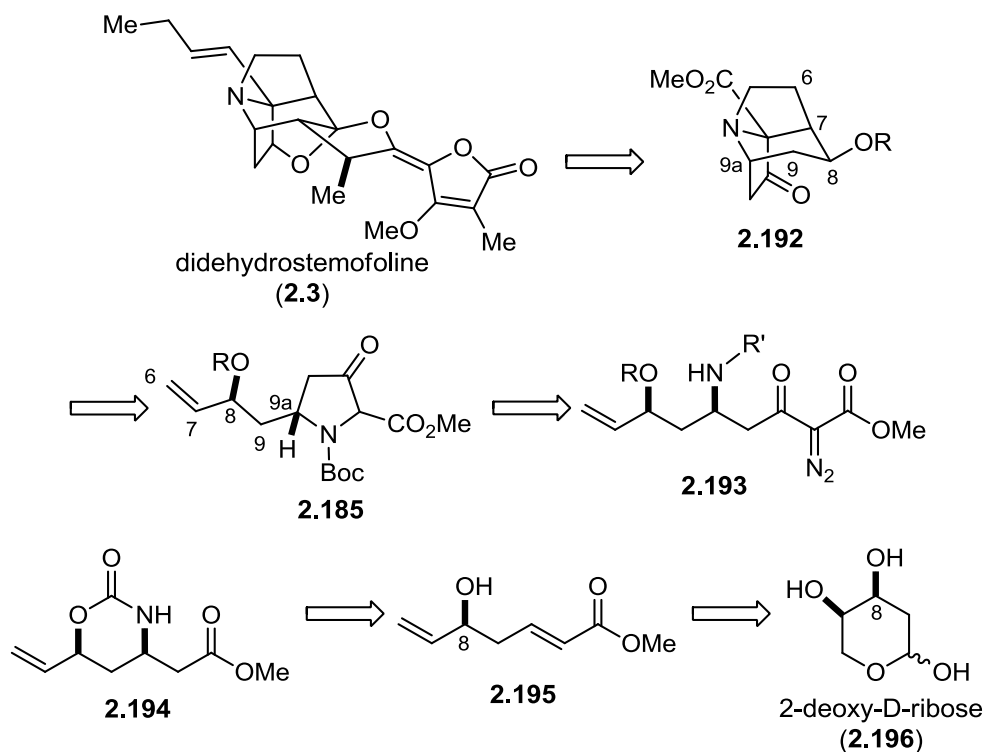
2.2.2 C(8)-Substituted Cycloaddition Substrate

2.2.2.1 Retrosynthesis

Limitations to the overall synthetic past strategies included the use of costly stoichiometric chiral auxiliaries and in some cases more than one. Also, due to lengthy and procedurally difficult synthetic sequences, the ability to advance material to the key cycloaddition addition step was cumbersome and limited further progress in the total synthesis. This early work, however, was seminal in establishing the viability of the key cycloaddition strategy for constructing the core of the target natural products. In redesigning our synthetic approach we hoped to access the tricyclic core of the stemofoline alkaloids by utilizing a “chiral pool” starting material. This tactic would provide key stereocenter(s) allowing for the remaining chirality to be built into the

molecule by utilizing substrate-controlled, diastereoselective strategies. As a result, this sort of approach would likely increase the overall efficiency of the synthesis by decreasing the number of synthetic operations. For this purpose, we chose the commercially available and affordable 2-deoxy-D-ribose (**2.196**) as our starting material as it possessed the required chirality and a majority of the carbon framework necessary to construct the tricyclic core (Scheme 2.35). The new strategy presented a number of challenges including: (1) The elaboration of 2-deoxy-D-ribose (**2.196**) into allylic alcohol **2.195**; (2) using allylic alcohol **2.195** to set up a diastereoselective aza-Michael reaction whereby the chirality of the allylic alcohol is directly utilized in setting the key nitrogen stereocenter to give **2.194**; (3) the selective functionalization of the resulting 1,3-aminoalcohol into the diazo compound **2.193**; and (4) discovery of cycloaddition conditions that are selective for the desired regioisomer **2.192**.

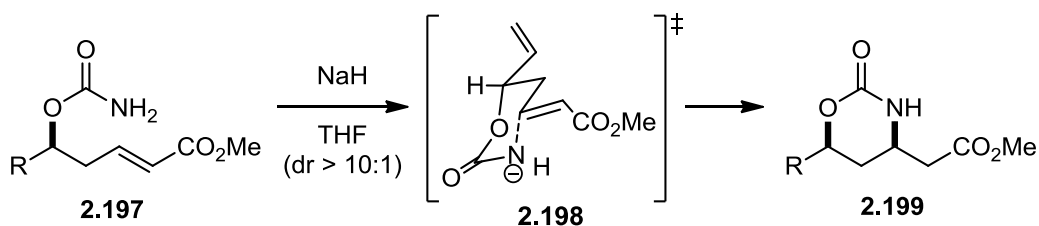
Scheme 2.35



In designing this route, we were cognizant of a method developed by Hirama and Ito for the stereoselective intramolecular aza-Michael reactions of primary carbamates tethered to enoates (Scheme 2.36).¹⁰⁴⁻¹⁰⁸ Hirama investigated an array of systems bearing homoallylic enoate alcohols, which could be converted in one step to the corresponding carbamates **2.197**. Treatment of structures such as **2.197** with base (either NaH or KO*t*-Bu) results in a facile cyclization via transition state **2.198** to give the corresponding cyclic carbamate **2.199** with high 1,3-*syn*-diastereoselectivities. The smallest R-group they investigated was a methyl group, which gave a diastereoselectivity of approximately 10:1. In other cases where the R-group was larger the observed diastereoselectivity could be as high as 95:5. We hoped to apply this reaction with a vinyl group as our R-group, which we expected to behave similar to the methyl-

substituted system. Adopting this methodology, we sought to use the chirality of the internal alcohol stereocenter of 2-deoxy-D-ribose and apply the Hirama cyclization to install the N-stereocenter in a 1,3-*syn* fashion. The dipolar cycloaddition event would then set the remaining stereocenters of the stemofoline core without the need to apply a single chiral auxiliary as was required with previous generations of our synthetic strategy.

Scheme 2.36

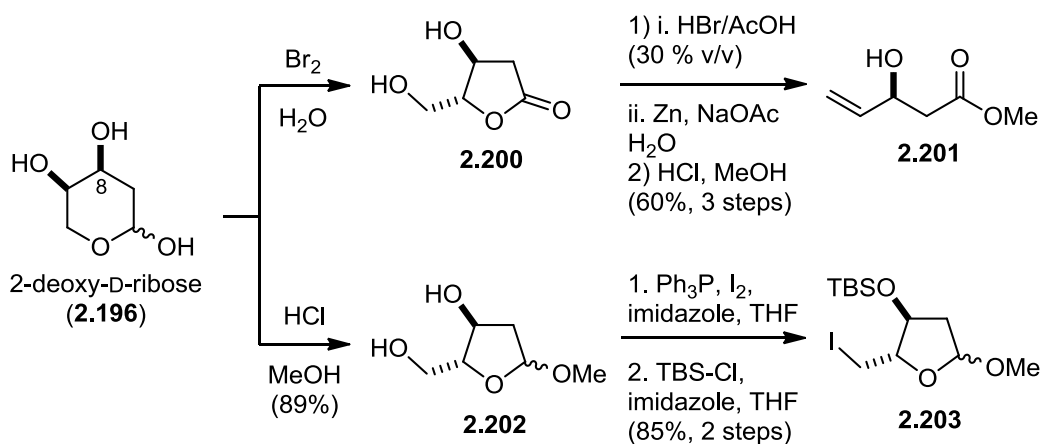


2.2.2.2 Synthetic Studies on the Conversion of 2-Deoxy-D-Ribose into Alcohol 2.195

The syntheses of ester **2.201** (Scheme 2.37)¹⁰⁹ and aldehyde **2.204** (Scheme 2.38)¹¹⁰ are both preceded and have been reproduced following slightly modified procedures than those reported in the literature. Starting from commercially available 2-deoxy-D-ribose (**2.196**), the ester **2.201** was accessed in three steps (Scheme 2.37). During the initial oxidation of **2.196**, the generation of catalytic amounts of acid facilitates the rearrangement to the intermediate five-membered lactol, which was then oxidized to the lactone **2.220**. The crude lactone **2.200** was treated with HBr/AcOH to form an acetylated primary bromide, which was treated with Zn, under buffered conditions, to furnish the corresponding acyclic carboxylic acid. The crude carboxylic acid, obtained after acid/base extraction, was esterified under Fisher conditions to provide the ester **2.201** in a 60% yield over the three step sequence.

Similarly, starting with 2-deoxy-D-ribose (**2.196**), the sugar can be refunctionalized by first performing an acid catalyzed isomerization to the five-membered lactol **2.202** in 89% yield (Scheme 2.37). Literature procedures for carrying out this sequence describe doing so on crude **2.202**;¹¹⁰ however, it was found that distillation of this intermediate resulted in cleaner reaction mixtures during subsequent steps. As such, purified **2.202** was then subjected to iodination conditions selective for the primary alcohol, and the resulting iodide was protected as its TBS-ether to give **2.203** in an 85% yield over two steps. It should be noted that the intermediate alcohol obtained after the iodination reaction was very unstable to light, especially in neat form. Attempts to perform the elimination directly by subjecting this intermediate to the Boord conditions, resulted only in complicated mixtures. Thus the protected silanol **2.303** was required.

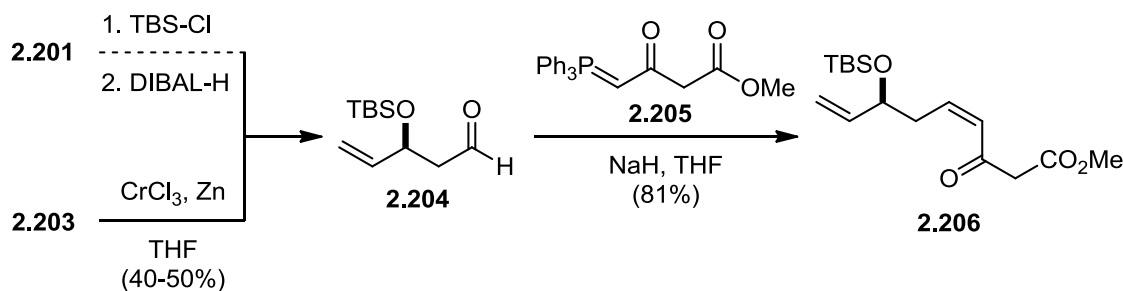
Scheme 2.37



The silyl ether **2.303** was then subjected to the reductive elimination step with chromium (II) chloride, which has been reported in the literature to be a mild reductant for this process (Scheme 2.38).¹¹⁰ Traditionally the Boord conditions call for the use of

zinc powder under aqueous conditions.¹¹¹ It has been reported, however, that for certain substrates performing the reaction under anhydrous conditions is often optimal. To that end, a number of anhydrous conditions have been developed including zinc-silver-graphite alloys, organometallic reagents, activated Zn in alcoholic solvents, and chromium (II) chloride.¹¹²⁻¹¹⁶ The exact elimination with CrCl_2 on compound **2.203** is known,¹¹⁰ so the chromium (II) was generated *in situ* by reduction of $\text{CrCl}_3 \cdot 3\text{THF}$ with zinc metal. However, the written procedure for this step is vague, and some complications arose in trying to repeat this reaction. The procedure references a number of different procedures for preparing $\text{CrCl}_3 \cdot 3\text{THF}$, but does not specify which procedure they opted to use. Also the literature procedure called for a 24 h reaction time, but it was found that stopping the reaction after 24 h resulted in reaction mixtures that yielded unclean **2.204**, even after chromatography. The literature procedure also failed to include necessary information as to the workup and isolation of the product, including chromatography conditions, which made initial success with this reaction difficult. It was eventually found that increasing the reaction time to ~48 h yielded much cleaner product. The likely explanation is that the starting material co-spots with the product, and due to the lower reactivity of CrCl_2 , not all starting material was consumed after 24 hours, making isolation of pure **2.204** by chromatography virtually impossible. Increasing the reaction time resulted in full conversion of the starting material, but lower than reported yields were still obtained (51% compared to the reported 83%). While this step has yet to be efficiently reproduced as described in the literature, enough of the crude aldehyde was obtained to screen some initial olefination conditions (Scheme 2.38).

Scheme 2.38

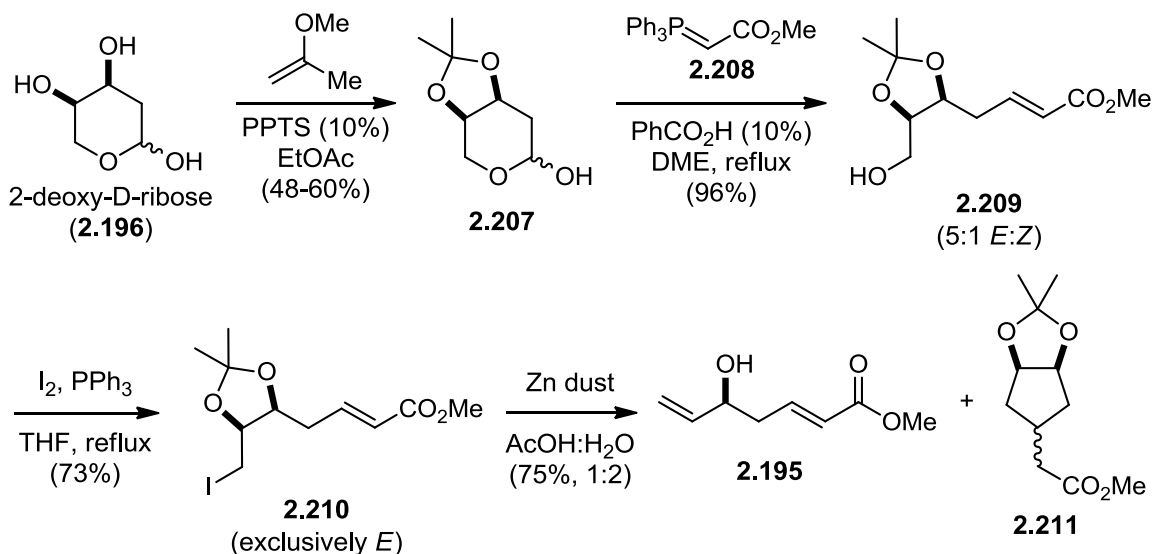


We initially attempted accessing the β -ketoester moiety directly so the Wittig reagent **2.205** was chosen. This reagent was found to be virtually unreactive with the aldehyde by itself and required activation as its sodium enolate (Scheme 2.38). The deprotonated Wittig reagent then behaved more like an unstabilized Wittig reagent and thus gave enone **2.206** as the *Z*-olefin. Attempts to remove the silyl protecting group resulted in complicated mixtures. While it can be conceived that an olefin isomerization could be used to give the *E*-olefin or another Wittig reagent could be used to access a simplified enoate rather than the β -ketoester, we were concurrently working on a complimentary strategy for advancing 2-deoxy-D-ribose. Thus we diverted our attention to a more fruitful strategy.

As indicated in the aforementioned retrosynthesis, we were ultimately interested in accessing the allylic alcohol **2.195**. The first generation synthesis began with the known protection of 2-deoxy-D-ribose (**2.196**) by treatment with 2-methoxypropene and PPTS to give acetonide **2.207** in variable yields (Scheme 2.39).¹¹⁷ The variable nature of this protection reaction was likely due to the insolubility of the sugar in the reaction solvent at the prescribed reaction concentration of 0.8 M. More consistent results were obtained with higher dilution of the reaction at 0.3 M, however, the product was always accompanied by the formation of the protected furanoside (5-membered) form of the

sugar. The protected lactol **2.207** was then subjected to a Wittig olefination to provide enoate **2.209** as a mixture (5:1 *E*:*Z*) of olefin isomers. Some initial effort went in to increasing the *E*/*Z*-ratio of the olefination event, specifically the use of the tributylphosphorane has been shown in our group to increase the diastereoselectivity of these types of olefinations.¹¹⁸ Applying these conditions to **2.207** resulted in an improved ~9:1 ratio. It is also known that molecular iodine can also catalyze thermodynamic equilibrations of enones and enoates,¹¹⁹ and since the impending iodination reaction required iodine we focused on this tactic. With this reactivity in mind, we used a 10 mol % excess of I₂ in the subsequent iodination of alcohol **2.209**, and found that the *E*/*Z*-ratio of 5:1 converged to the more thermodynamically stable *E*-olefin during the iodination of the primary alcohol to provide exclusively iodoenoate **2.210** in 73% yield. Compound **2.210** was then treated with activated Zn (dust)/AcOH, resulting in a facile Boord elimination to give a mixture (1:2) of the desired allylic alcohol **2.195** and cyclopentane **2.211** in 75% yield. The formation of the cyclic product **2.179** was unexpected in this reaction as it is not typical for organozinc compounds to undergo such facile 1,4-addition. However, it was even more surprising that in this case the cyclization reaction vastly outcompeted the presumably more entropically favored elimination process. Although this first generation approach was far from optimal, it provided the necessary alcohol **2.195** in 10% overall yield requiring four synthetic steps and four chromatographic purifications.

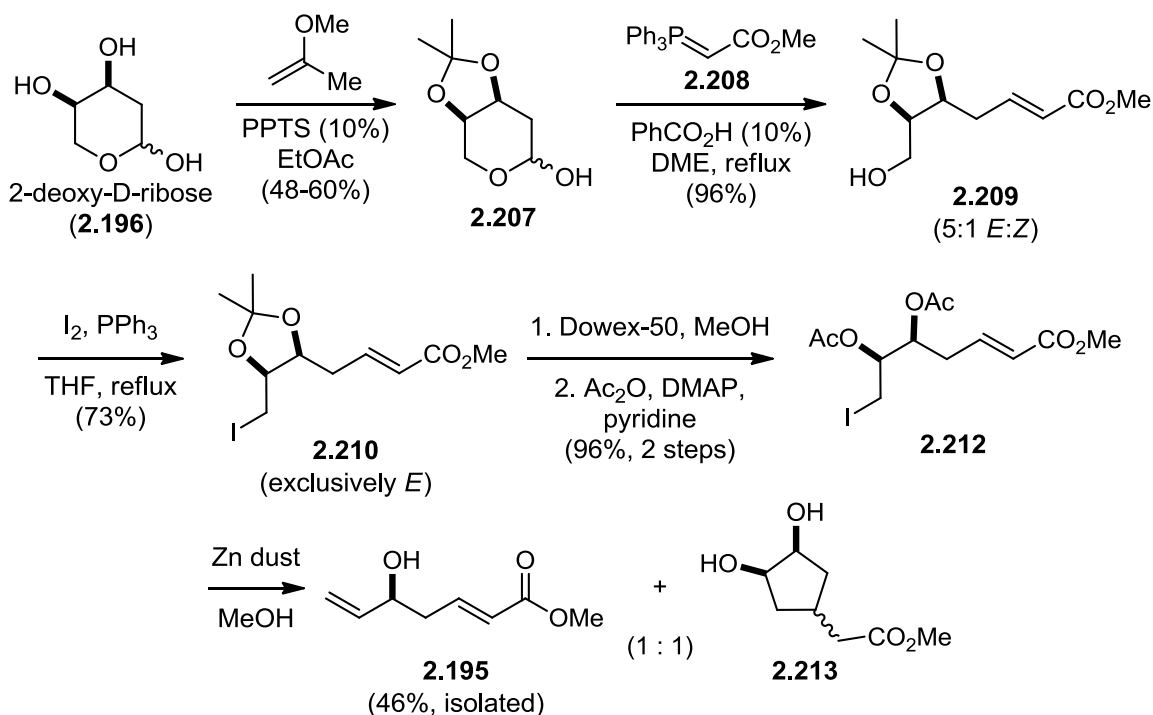
Scheme 2.39. 1st Generation Synthesis of 2.195: 4 Steps, 4 Columns, 10% Overall Yield



Initial success in accessing **2.195** provided us with an avenue to test later chemistry in the total synthesis; however, there was a synchronized effort to optimize the synthesis of allylic alcohol **2.195**. The overall efforts to prepare **2.195** have progressed through a number of discrete synthetic generations. Improvements to the overall process were continually measured by the overall yield (from **2.196**), number of steps, number of days that the sequence took to complete, and the number of chromatographic purifications that were required to provide **2.195** in pure form. We therefore hypothesized that the Boord elimination of acetone **2.210** might be improved by refunctionalizing the diol to increase the leaving group ability of the alcohol beta to the organozinc and consequently favor more of the desired elimination (Scheme 2.40). To that end, a second generation synthesis of **2.195** was devised in which the acetone of **2.210** was converted to **2.212** in 96% yield by treatment with Dowex/MeOH and acetylation. Subjecting iodide **2.212** to the Boord elimination with Zn (dust)/AcOH

resulted in an improved ratio (1:1) of elimination and cyclization products as their acetylated derivatives. It was subsequently discovered when elimination with Zn (dust) was performed in methanol rather than AcOH elimination and concomitant transesterification occurred to deliver alcohol **2.195**, along with an equimolar amount of diol **2.213**. These improvements thus provided **2.195** in a slightly improved 16% overall yield from the previous 10%, but required six synthetic operations and four chromatographic purifications. It was confirmed, however, that the Boord elimination could be further favored by adjusting the leaving group ability of the beta substituent.

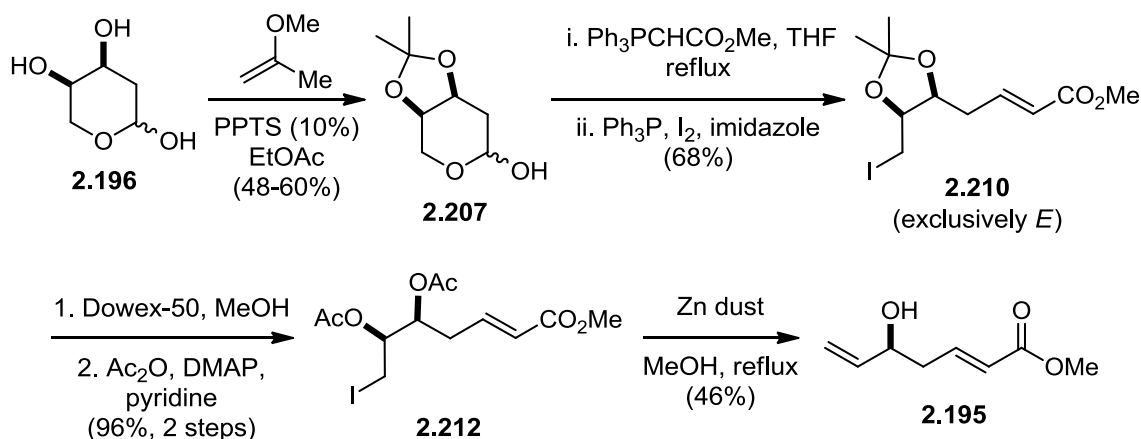
Scheme 2.40. 2nd Generation Synthesis of 2.195: 6 Steps, 4 Columns, 16% Overall Yield



Many attempts were made to telescope different procedures in order to cut down on the number of steps and purifications that were required to synthesize **2.195**. In that

context, we discovered that the olefination and the iodination reactions could be performed as a one-pot procedure by simply adding the reagents for the second transformation to the flask upon completion of the first operation, thus providing iodide **2.210** in 68% yield from **2.207** (Scheme 2.41). This simple change provided a route that cut off one synthetic step, one chromatographic purification, and ~24 h from the overall process. The overall yield of the sequence, however, remained roughly the same as the second generation approach.

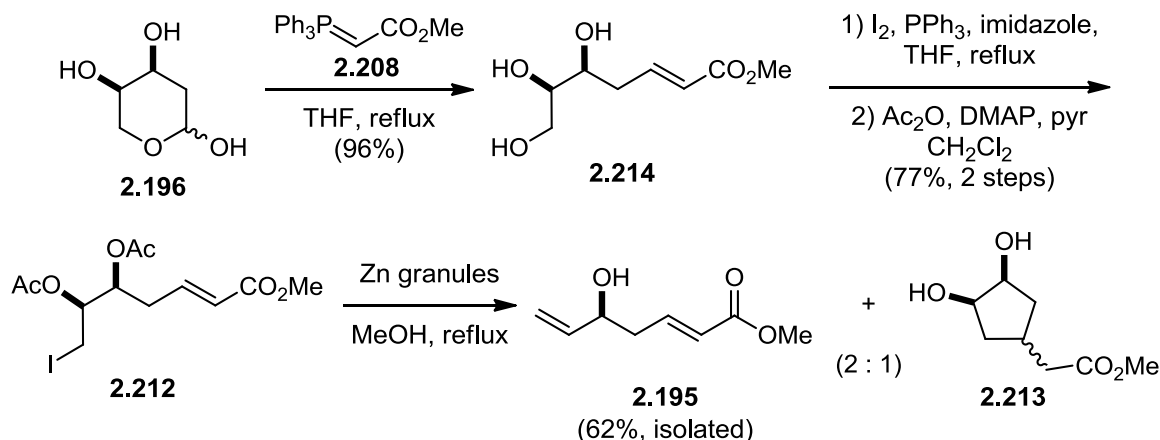
Scheme 2.41. 3rd Generation Synthesis of 2.195: 5 Steps, 3 Columns, 18% Overall Yield



In the interest of further streamlining the synthesis, the diol protection strategy was more closely scrutinized. It was known that 2-deoxy-D-ribose itself undergoes olefination without protection.¹²⁰ Accordingly **2.196** was treated with Wittig reagent **2.208** directly to give enoate triol **2.214** in 96% yield (Scheme 2.42). The primary alcohol could then be selectively manipulated in a variety of different ways. For example, iodination of **2.214** followed by acetylation of the intermediate iodo diol provided iodo diacetate **2.212** in 77% over two steps. The use of Zn granules, rather Zn

dust, improved the elimination reaction and provided product **2.195** in an improved 62% yield. This result bears further consideration because it is not clear why the physical state of the Zn would so drastically affect the product distribution. This may suggest that trace metal impurities (such as copper) might affect the elimination reaction, placing importance on the source of the zinc metal. This increase in product ratio and isolated yield, however, has been repeated many times on reaction scales up to 50 g, and thus we are confident in the viability of this process. This third generation of the synthesis provided **2.195** in a much improved 45% overall yield and cut out one synthetic step and one chromatographic purification. Furthermore, as a result of these improvements, the overall process of converting 2-deoxy-D-ribose into alcohol **2.195** was reduced by >48 h from the previous generation.

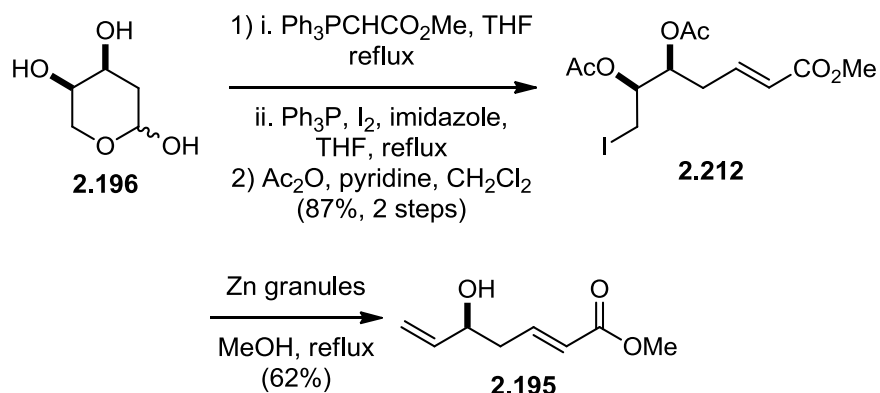
Scheme 2.42. 4th Generation Synthesis of 2.195: 4 Steps, 2 Columns, 45% Overall Yield



The synthetic process was fully optimized by capitalizing on the previously discovered tandem olefination/iodination strategy, but this time the procedure was performed on the unprotected sugar (Scheme 2.43). Using this protocol, the synthesis of

the allylic alcohol **2.195** was shortened to three chemical operations, requiring only one chromatographic purification, and less than three days to provide the allylic alcohol **2.195** in approximately 54% overall yield. With this optimized protocol in place, the first crucial chiral intermediate in the synthesis was easily obtained in pure form.

Scheme 2.43 Optimized Synthesis of 2.195: 3 Steps, 1 Column, 54% Overall Yield

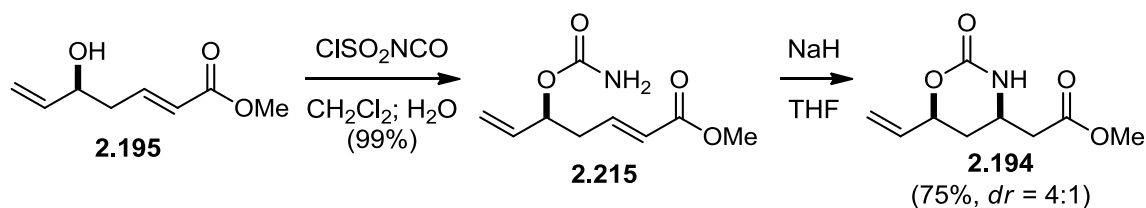


2.2.2.3 Synthetic Studies on the Application of the Hirama-Ito Cyclization to Construct the 1,3-*syn*-Aminoalcohol Moiety

With an efficient, scalable route to the allylic alcohol **2.195**, the Hirama-Ito cyclization was applied to construct the critical 1,3-aminoalcohol moiety. The allylic alcohol **2.195** was first treated with chlorosulfonylisocyanate to give the primary carbamate **2.215** in nearly quantitative yield after a hydrolytic workup (Scheme 2.44). Compound **2.215** was treated with NaH at room temperature to give the cyclic carbamate **2.194** in 75% yield and as a mixture (4:1) of *syn*- and *anti*-diastereomers via an intramolecular aza-Michael reaction. Thus, the chirality of the alcohol could be exploited in a substrate controlled assembly of the eventual C(6)-nitrogen stereocenter. We were nevertheless intrigued by the possibility of optimizing of this process in the hopes that we

could increase the diastereoselectivity. Although the primary reports by Hirama indicated that the yield and diastereoselectivities could not be affected by changes in solvent and temperature, however, we found that a number of variables impacted the yield and diastereoselectivity of this process.

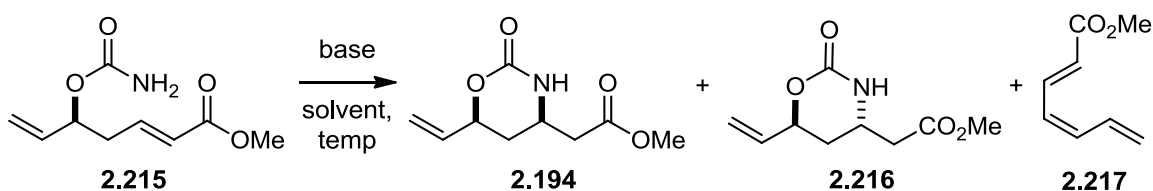
Scheme 2.44



Some of our findings regarding the optimization of the Hirama cyclization method are outlined in Table 2.1. The elimination product **2.217** was always observed in these reactions, although not always quantified. This elimination has not been reported in any of the accounts by Hirama, but this side reaction often accounted for nearly 10-20% of the product distribution in our system. It was found that elimination was enhanced when using more polar solvents, with DMF providing upwards of 20% of **2.217**. Although not a standard solvent with NaH , the use of CH_2Cl_2 provided only trace amounts of the triene and provided good reactivity of NaH at lower temperatures. The use of NaH in THF did not provide appreciable conversion at low temperature, but in CH_2Cl_2 the reactions were complete within 4 h. Although temperature had no effect on the elimination amount, the diastereoselectivity did show remarkable response to changes in this variable. At temperatures of $-20\text{ }^\circ\text{C}$ and below, the diastereoselectivity peaked at 10:1. We also tested the counterion effects in this reaction and found that more Lewis acidic counterions led to increasing amounts of elimination, but the Lewis acidities had no influence on the diastereoselectivity. In the case of $\text{KO}t\text{-Bu}$ at $-40\text{ }^\circ\text{C}$ (Table 2.1,

Entry 3), the diastereoselectivity (10:1) was good, but freshly sublimed base was required for obtaining high yields. With NaH and CH₂Cl₂, the reaction at -10 °C gave a slightly lower diastereoselectivity (8:1), but gave the cleanest reaction mixtures of any of those screened. This allowed the product to be isolated from the reaction mixture very efficiently by recrystallization. No other set of conditions we screened allowed for direct crystallization of the product because of the higher level of impurities in the reaction mixtures, and thus required chromatography. As a result, the use of NaH in CH₂Cl₂ at -10 °C (Table 2.1, Entry 7) was determined to be the best overall conditions for preparing **2.161**.

Table 2.1



Entry	Base	Solvent	Temp (°C)	Yield (%)	Selectivity
1	NaH	THF	25	75	4 : 1, <i>syn:anti</i> (~10% elimination)
2	KH	THF	- 40	74	10 : 1, <i>syn:anti</i>
3	KOt-Bu	THF	- 40	78	10 : 1, <i>syn:anti</i>
4	LiOt-Bu	THF	- 40	N.D.	only elimination observed
5	NaH	DMF	0	N.D.	4 : 1, <i>syn:anti</i> (~20% elimination)
6	NaH	CH ₂ Cl ₂	0	80	7 : 1, <i>syn:anti</i> (~3% elimination)
7	NaH	CH ₂ Cl ₂	- 10	80	8 : 1, <i>syn:anti</i> (~3% elimination)

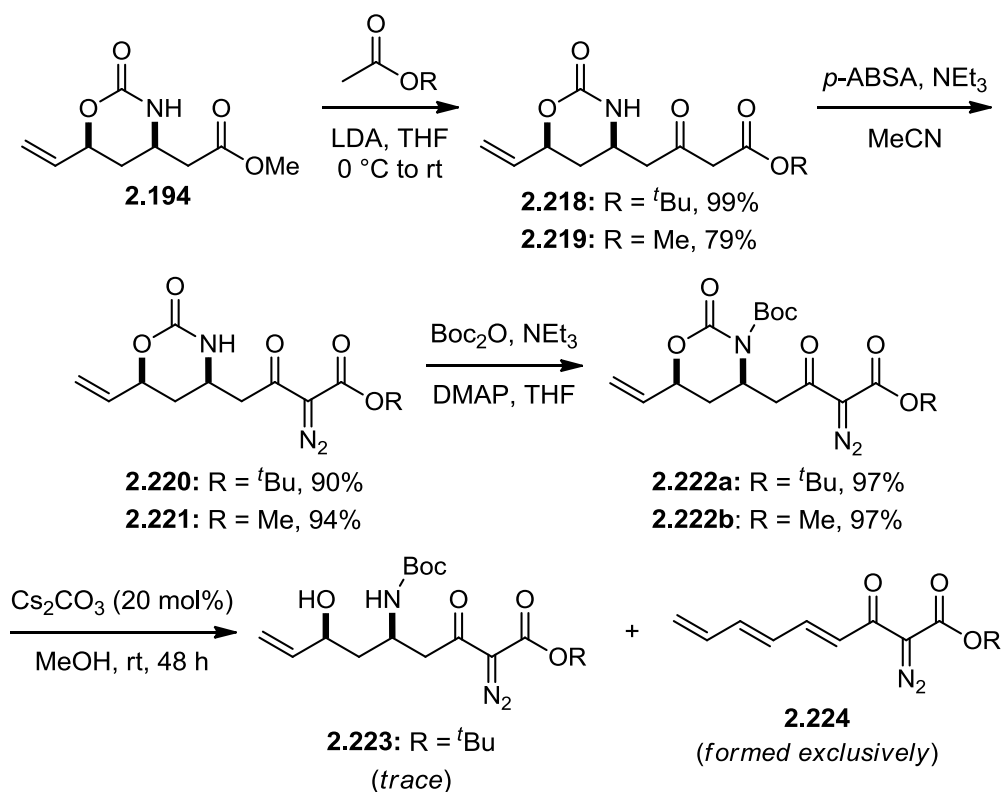
*reactions at 0 °C and rt had larger amounts of elimination and were therefore not quantified

2.2.2.4 Installation of the Diazo-β-ketoester Moiety

With a scalable synthesis of carbamate **2.194** at our disposal, we next turned our attention to accessing an orthogonally protected amino alcohol bearing the required diazo-β-ketoester moiety. This task, however, proved to be more troublesome than

anticipated, and a number of different tactics were ultimately considered. Conditions for removing the cyclic carbamate needed to be identified, but it was unclear at what stage it would be optimal to do so. Carbamates of this type are notoriously difficult to cleave by means of nucleophilic addition, and, as such, the nitrogen atom has to be acylated to activate the cyclic carbamate to nucleophilic attack.

Scheme 2.45



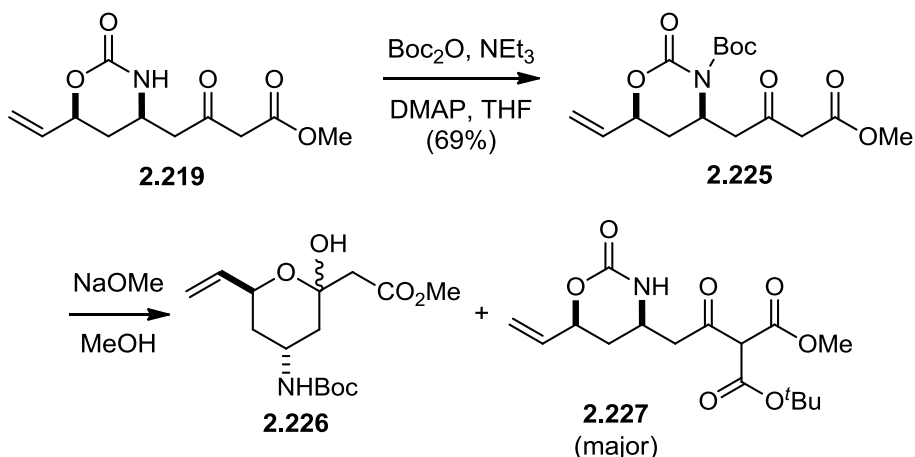
We first decided to explore elaborating ester **2.194** into the corresponding β -ketoesters **2.218** or **2.219** (Scheme 2.48). The cross-Claisen reaction would therefore occur before refunctionalizing the amino alcohol. To obtain good conversions, the reaction was warmed to room temperature upon complete addition of the enolate to a solution of **2.194** and provided the β -ketoesters in good yield. Originally the use of *t*-

butyl acetate was studied due the enolate of this ester being easier to form in high conversion and allowed access to **2.218** in 99% yield. The use of methyl acetate was also studied since we realized that the *t*-butyl ester of **2.218**, and its subsequent derivatives, would be incompatible with conditions later in the synthesis. The cross-Claisen with the enolate of methyl acetate, however, was lower yielding than with *t*-butyl acetate providing **2.219** in only 79% yield. Diazo transfer on **2.218** and **2.219** with *p*-ABSA then delivered the corresponding diazo- β -ketoesters **2.220** and **2.221** in high yields. Next, the cyclic carbamates were activated by acylation of the nitrogen atom as the *t*-butyl carbamate to give **2.222a** and **2.222b** in >95% yields, and cleavage of the cyclic carbamate was attempted using catalytic amounts of Cs₂CO₃ in methanol. Surprisingly the acidic nature of the α -protons of the diazo- β -ketoester **2.222a** proved troublesome as rapid enolization and elimination of the biscarbamate moiety occurred to give the highly conjugated diazo compound **2.224** as the major product. This result clearly indicated that the cyclic carbamate would have to be cleaved at a stage prior to the installation of the diazo moiety.

Based on the previous result, we anticipated that β -ketoester **2.225** would be a better substrate for the carbamate cleavage reaction due to the likely preference of the β -ketoester moiety to be enolized under the basic reaction conditions (Scheme 2.46). We felt that if the β -ketoester was fully enolized during the cleavage reaction, then the possibility of elimination of the biscarbamate would be removed due to the inability of the ketone to enolize on the side opposite the ester. Subjecting **2.225** to cesium carbonate in methanol, however, gave a complex product mixture. We therefore decided that in order to further enforce the enolization of **2.225**, excess sodium methoxide would be superior to catalytically generated cesium methoxide. Activation of the carbamate **2.219** as its *t*-butyl carbamate **2.225** then set up the methanolysis step. Treatment of **2.225** with three

molar equivalents of sodium methoxide in MeOH partially cleaved the cyclic carbamate to provide what was tentatively assigned as **2.226**, but a significant amount of an inseparable byproduct was formed that was tentatively assigned as the tricarbonyl compound **2.227**. The ^1H NMR spectrum showed that two products were present and both still had the *t*-butyl group intact. Also present in the NMR spectrum was a sharp singlet at ~6 ppm indicative of the NH of the deprotected cyclic carbamate, and a significant enol (OH) signal at ~12 ppm. Furthermore, compound **2.226** has been authenticated by subsequent experiments, and it was clear by analysis of the NMR spectrum that this was not the major product. It was presumed therefore that the enolate of **2.225** attacked the adjacent Boc-group through a 6-membered transition state resulting in acyl-transfer to the β -ketoester moiety. Once the Boc-group was removed from the cyclic carbamate, it is no longer susceptible to methoxide cleavage and thus compound **2.227** was tentatively assigned as the major product.

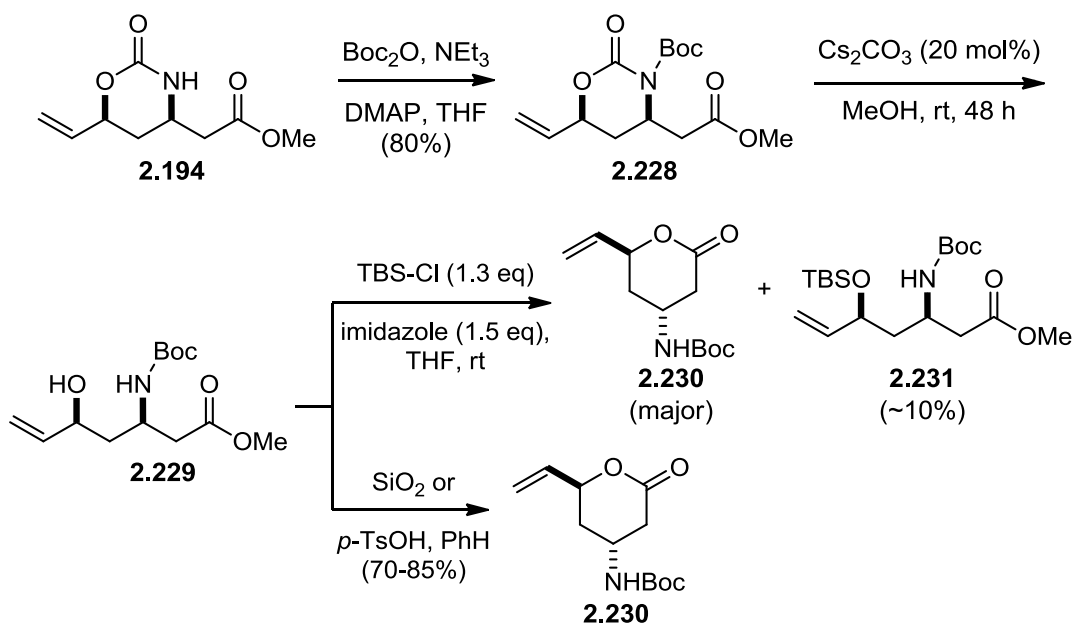
Scheme 2.46



Finally, we considered cleaving the cyclic carbamate at an earlier stage before any attempts were made to elongate the carbon chain to the β -ketoester. Thus, **2.194** was

converted to its Boc-carbamate **2.228** in 80% yield (Scheme 2.47). Carbamate **2.228** was then subjected to the standard methanolysis conditions, using Cs₂CO₃/MeOH to cleanly deliver the desired untethered amino alcohol **2.229**. This intermediate was observed by NMR and TLC; however, attempts to purify this compound by silica gel chromatography resulted in mostly lactonization to give **2.230**. This process could also be initiated by treatment of the crude amino alcohol **2.229**, after workup, with *p*-toluenesulfonic acid in benzene. In the interest of preventing the lactonization, we also looked at protecting the crude amino alcohol as its TBS-ether. Under the initial conditions screened, only trace amounts of the desired silanol **2.231** were observed. Interestingly, these conditions also facilitated the lactonization process. At this point we decided to try to utilize the lactone intermediate since we saw the lactone as a reasonable substrate for the impending Claisen reaction to give the desired β -ketoester moiety.

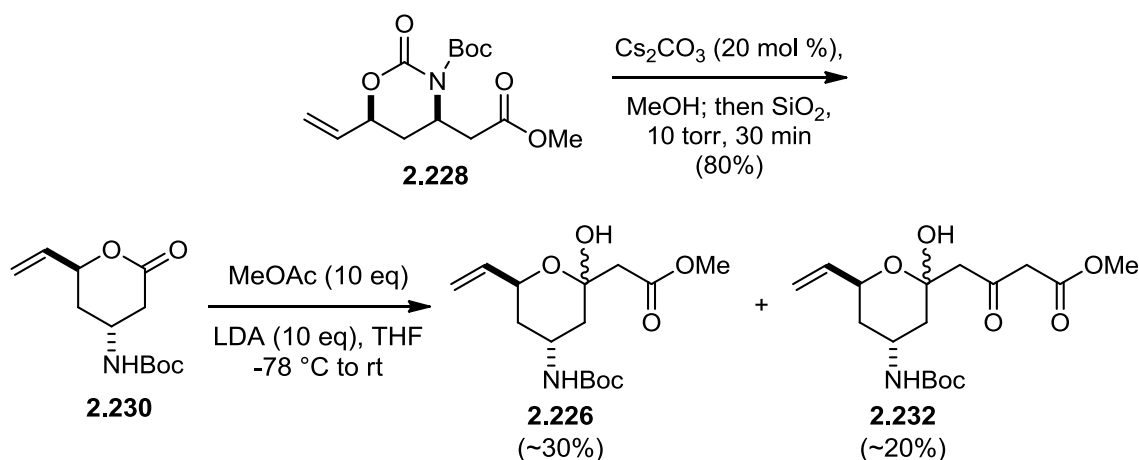
Scheme 2.47



Attempts to optimize the lactonization process using various combinations of acid catalysts, solvents, and additives led to the discovery that pre-adsorbing the crude amino alcohol **2.229** on SiO₂ before the chromatography step and drying the SiO₂ under high-vacuum for 30 min, resulted in a facile lactonization to give lactone **2.230** in 80% yield from the biscarbamate **228** (Scheme 2.48). The Claisen reaction was then performed on **2.230** with the enolate of methyl acetate to furnish approximately 30% yield of **2.226** along with the unexpected multiple addition product **2.232** in approximately 20% yield. This reaction was subject to a great deal of scrutiny and optimization; however, under all conditions screened this still represents the best result. Attempting to lower the equivalencies of MeOAc and LDA only resulted in lower yields of the desired product. At temperatures below -20 °C, there was no appreciable enolate addition due to the mechanistic requirement of adding the enolate to the already deprotonated carbamate anion. Holding the reaction at 0 °C for extended periods of time only resulted in increased amounts of **2.232** relative to the desired product. The formation of **2.232** is a very unusual observation, since typically it is believed that the Claisen reaction, upon delivering the initial β -ketoester product, will result in a rapid enolization of the acidic β -ketoester and thus no further enolate addition will occur. In our system, however, the product that results after the initial enolate addition is presumably the dianion of **2.226**, not the expected linear β -ketoester form. Since the initial addition reaction requires elevated temperature, it is presumed that an extra equivalent of enolate adds to the dianionic ester to give **2.232**. In all cases this reaction was not clean, and a number of unidentified products were always formed. Fortunately, the desired product was much less polar than any of these products. Purification of **2.226** by chromatography proved difficult and, despite our best efforts, the methyl acetoacetate byproduct (formed from a homo-Claisen process during enolization of methyl acetate) partially co-eluted with the

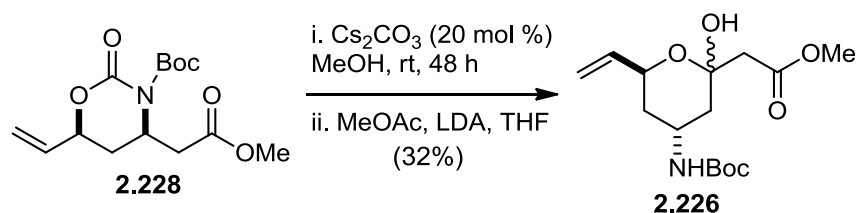
product in all solvent systems that were screened. Attempts were made to fully remove the methyl acetoacetate byproduct before purification, but the lactol product **2.226** proved too unstable to hold under high-vacuum for extended periods of time. Thus, **2.226** was typically taken on to the next step with variable amounts of methyl acetoacetate contaminants

Scheme 2.48



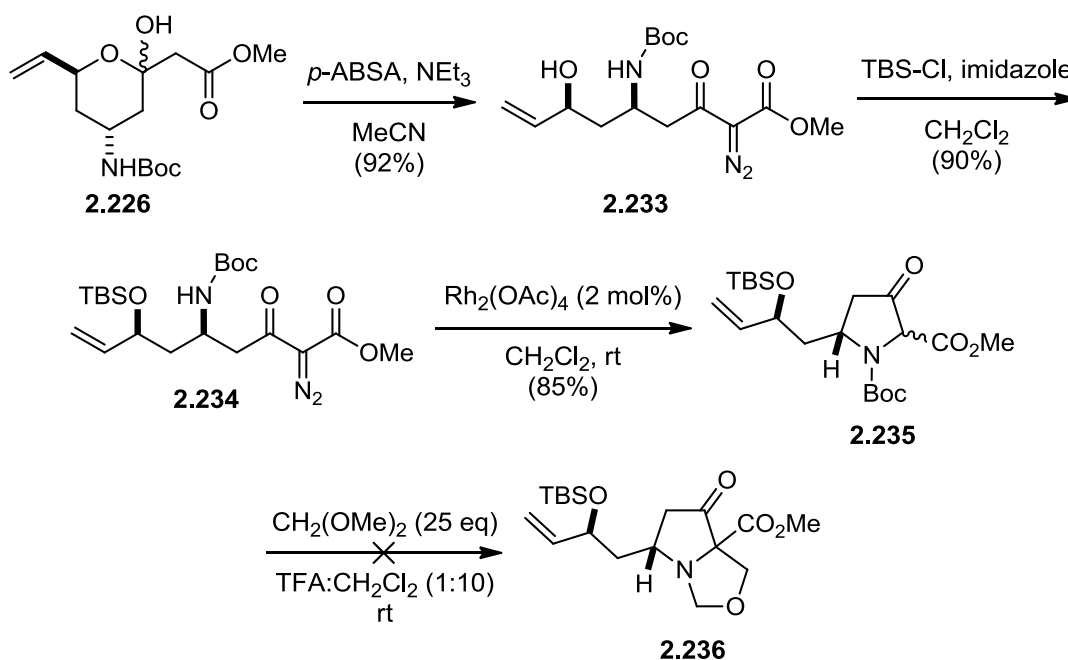
Despite the low efficiency of the above-mentioned Claisen reaction, we were still able to prepare a crucial intermediate for subsequent studies. One additional operational improvement that deserves mention was the realization that the crude amino alcohol **2.229** could be subjected directly to the Claisen reaction after removal of the methanol solvent from the previous step, and provided comparable yields of **2.226** to the preformed lactone **2.230** (Scheme 2.49). Accordingly, the biscarbamate **2.228** was subjected to methanolysis, and once carbamate cleavage was complete, the mixture was concentrated. The residue was directly subjected to the Claisen reaction to give **2.226** in 32% overall yield. This process managed to improve the overall yield by about 8% on average, but more importantly it greatly simplified the overall procedure for preparing **2.226**.

Scheme 2.49



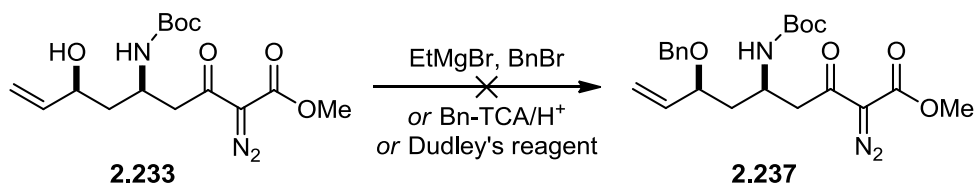
With enough lactol **2.226** in hand, we focused on proceeding forward to the cycloaddition step. Subjecting lactol **2.226** to a diazo transfer reaction gave the acyclic diazo- β -ketoester **2.233** in 92% yield (Scheme 2.50). Protection of the allylic alcohol **2.233** as its TBS-ether proceeded smoothly to give compound **2.234** in 90% yield, which was subjected to a rhodium catalyzed NH-insertion reaction to give pyrrolidinone **2.235** in 85% yield. All attempts to elaborate **2.235** into oxazolidine **2.236**, however, proved fruitless. While the exact product distribution of this reaction was never fully established, it was determined that loss of the TBS-group was very rapid. Considering that the oxazolidine formation conditions likely generate a great deal of methanol by decomposition of dimethoxymethane, it is not surprising that the conditions of excess TFA/MeOH resulted in the loss of the silyl protecting group. With this in mind, we began looking at a more robust protecting group to install prior to the oxazolidine formation step.

Scheme 2.50



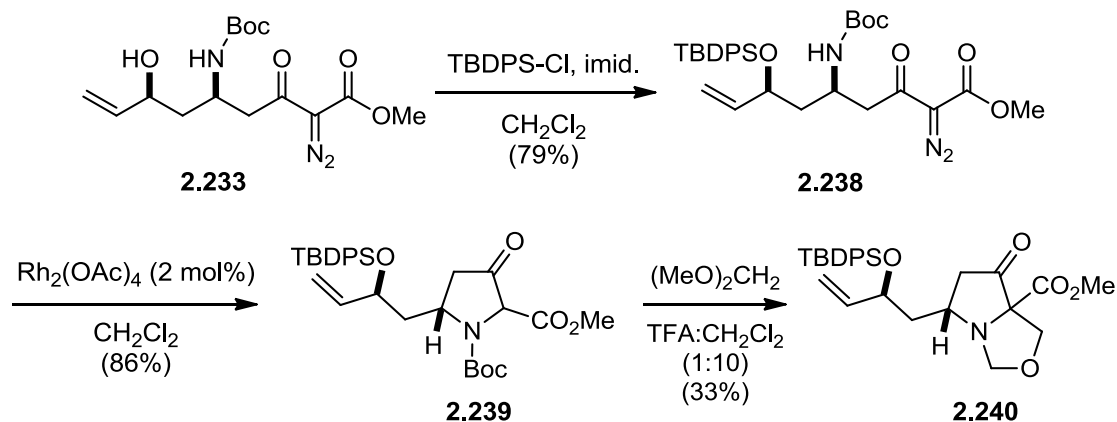
Initially we looked at benzyl protection of the allylic alcohol **2.233**, and after a thorough literature search it became clear that the selective *O*-alkylation of the 1,3-amino alcohol would not be trivial. We spent a good deal of time screening various conditions including standard alkylation conditions with benzyl bromide (Scheme 2.51). Attempts to form the dianion resulted in rapid decomposition of the starting material delivering only complex mixtures. Benzyl trichloroacetimidate (Bn-TCA) with a camphorsulfonic acid catalyst proved unreactive, whereas the use of a triflic acid catalyst led to complex mixtures presumably exacerbated by loss of the Boc-group. Finally, the use of Dudley reagent (2-benzyloxy-1-methylpyridinium triflate) was investigated, but no reaction was observed at ambient temperature, and complex mixtures resulted under more forcing conditions.

Scheme 2.51



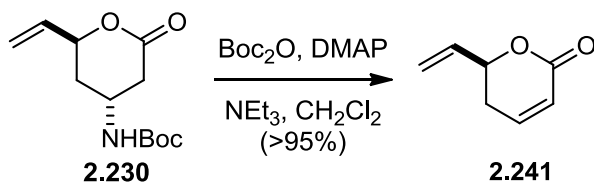
Considering that silylation had proven effective for protecting the allylic alcohol, we next tried to install a TBDPS-group hoping that this group would at least be stable enough to allow for some of the desired oxazolidine formation (Scheme 2.52). Reacting alcohol **2.233** with TBDPS-Cl and imidazole furnished the silyl protected alcohol **2.238** in 79% yield. Reaction of **2.238** with rhodium supplied pyrrolidinone **2.239** in 86% yield. Gratifyingly, the oxazolidine synthesis was effective at delivering the cycloaddition precursor **2.240** under standard conditions with dimethoxymethane and TFA, albeit in low yield. The initial synthesis of **2.240** provided enough material to test the cycloaddition (see Section 2.2.2.5); however, our efforts to optimize the step leading up to the key cycloaddition were far from over. We felt that having a scalable route up to the cycloaddition step would not only be critical for optimizing and eventually solving the cycloaddition step, but would also provide ample material to begin advancing the synthesis beyond this key step. Thus we continued our efforts of optimizing the foundation of our total synthesis.

Scheme 2.52



The inefficiency of the Claisen reaction to install the β -ketoester moiety to provide **2.226** was troublesome, and thus our approach was revisited. We reasoned that by doubly protecting the carbamate of **2.230** we could potentially lower the energy required to complete the enolate addition to the lactone since an anion of **2.230** would not be formed (Scheme 2.53). We felt that by accessing a more reactive Claisen substrate that a cleaner and more selective reaction would result. To that end, attempts to additionally protect **2.230** as the corresponding biscarbamate, thereby eliminating the acidic hydrogen atom, only resulted in a facile elimination reaction giving the α,β -unsaturated lactone **2.241** in virtually quantitative yield.

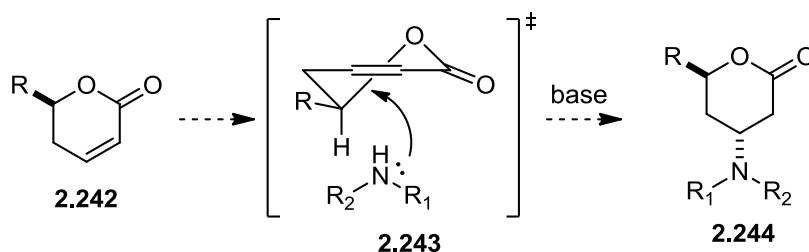
Scheme 2.53



This elimination reaction (Scheme 2.53) raised our awareness of methods in the literature that accomplished highly stereoselective aza-Michael reactions on substrates

similar to **2.242** with amino nucleophiles (Scheme 2.54). We therefore postulated that if we could prepare **2.241** more directly, an aza-Michael reaction could be utilized where the diastereoselectivity of this transformation was controlled merely by the stereoelectronics of the 6-membered transition state such as **2.243** (Scheme 2.54). In the proposed transition state, the vinyl group in the 6-position would be positioned equatorially and thus axial attack of the incoming nucleophile would give the desired 1,3-*anti*-relationship (i.e. **2.244**). In considering this transformation, a number of literature examples on similar sugar-derived lactones such as **2.242** became apparent and gave very encouraging precedent for this strategy moving forward.¹²¹⁻¹²⁵ This strategy would be more modular allowing direct access to amino lactones such as **2.244** bearing appropriate functionalization at R₁ and R₂ based on the amino nucleophile chosen. In this way a series of Claisen substrates could be synthesized to help improve the enolate addition step. Also, by accessing an amine such as **2.244** rather than the more acidic carbamate **2.230**, double protection of the nitrogen atom would most likely not be required because of the effective increase of the pK_a of the nitrogen-hydrogen bond.

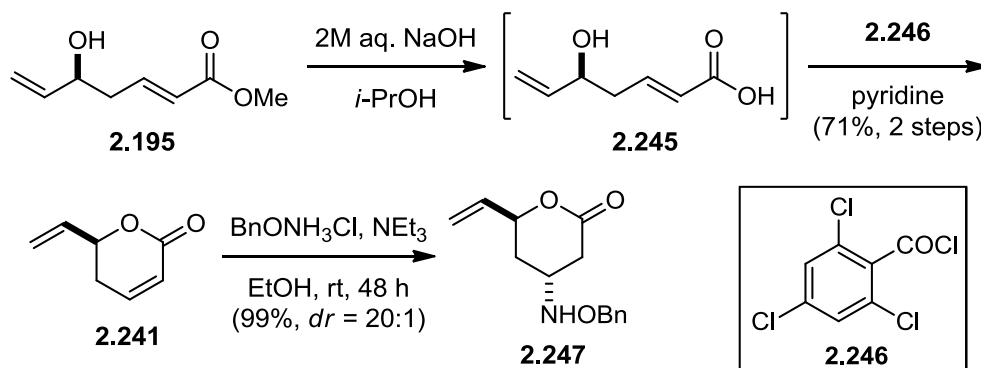
Scheme 2.54



By modifying the key step for installing the *N*-stereocenter, a new route could be devised to access lactone **2.241** in a more rapid fashion than was previously possible (Scheme 2.55). Fortunately, allylic alcohol **2.195** was still envisioned as an intermediate

en route to lactone **2.241**, and thus all the prior effort put into optimizing the synthesis of **2.195** would still be constructive. Thus, saponification of **2.195** followed by a known isomerization/lactonization protocol using Yamaguchi reagent (**2.246**) and pyridine provided the α,β -unsaturated lactone **2.241** in 71% yield over two steps.¹²⁶ The key aza-Michael reaction was then performed using *O*-benzyl hydroxylamine as the nucleophile. Gratifyingly, not only did the reaction proceed in virtually quantitative yield, but the diastereoselectivity (20:1 *anti:syn*) was higher than the Hirama-Ito strategy that gave at best a 10:1 ratio (*cf.* Table 2.1). It is also important to note that the product of the aza-Michael reaction was sufficiently clean that no additional purification was required after removal of the salts by trituration with ethyl ether.

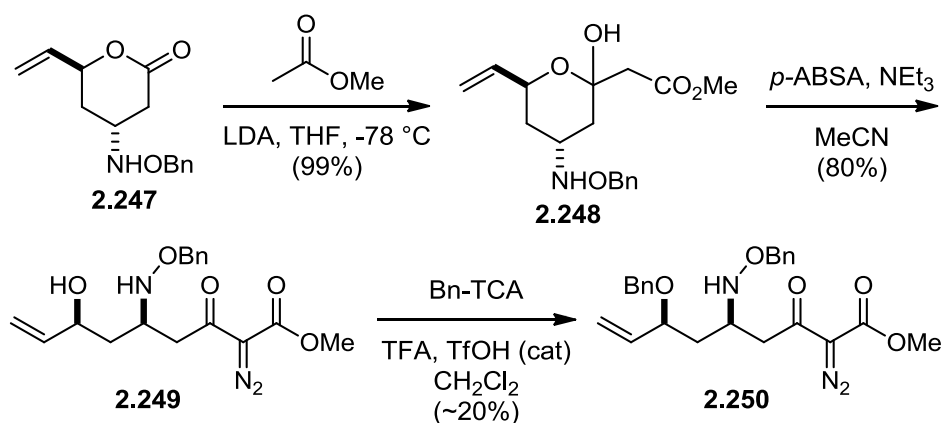
Scheme 2.55



We next tested the hypothesis that the use of an amine rather than a carbamate in the Claisen reaction would increase the efficiency of the reaction by raising the pK_a of the NH-bond, thus resulting in a more facile enolate addition (Scheme 2.56). In the event, the Claisen reaction of **2.247** gave amino lactol **2.248** in virtually quantitative yield and high purity after only an acid/base extraction. The diazo transfer of lactol **2.248** then furnished diazo- β -ketoester **2.249** in 80% yield, which again was effectively purified by

acid/base extraction. In comparing the synthesis of **2.249** with that of the comparable diazo- β -ketoester **2.233** from the previous generation of this synthesis, it is clear that a number of significant improvements have been made. The process for preparing **2.249** was much more selective and, as a result of accessing basic amino derivatives, removed three chromatographic purifications. Also, the increased efficiency of the Claisen reaction amounted to a much higher overall yield. The challenge of cleaving the N,O-bond and functionalizing the amino alcohol was still unsolved, however, and without an obvious procedure for accomplishing this it was not clear that this strategy was yet viable.

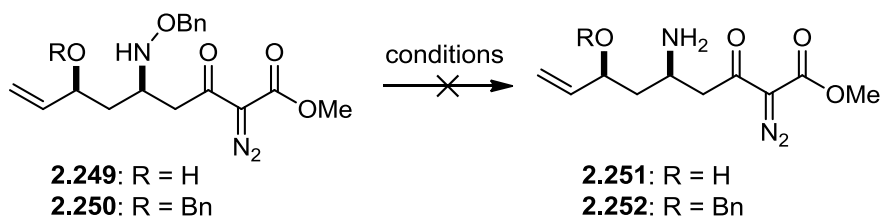
Scheme 2.56



With the acidity of the NH-bond now lowered, we reasoned that it should be possible to stoichiometrically generate the alkoxide anion and selectively alkylate with a benzyl electrophile. Unfortunately, the generation of the sodium alkoxide with NaH at room temperature resulted in rapid decomposition of the starting material. Although the reaction mixture was complicated, it appeared that **2.247** was forming during the reaction, presumably the product of attack of the alkoxide on the ketone followed by

expulsion of methyl diazoacetate anion. Performing the deprotonation at $-78\text{ }^{\circ}\text{C}$ with ethyl magnesium bromide or *n*-BuLi proved mild enough for the diazo β -ketoester, however, no alkylation was observed using benzyl bromide at this temperature. Attempts to alkylate **2.249** under acidic conditions using benzyl trichloroacetimidate (Bn-TCA) were somewhat successful. Amino alcohol **2.249** was treated first with trifluoroacetic acid to pre-form the amine salt, thus rendering the nitrogen atom unreactive to alkylation. Treatment of the amine-TFA salt with Bn-TCA, in the presence of various acid catalysts, provided the benzyl ether **2.250** only in low yields along with recovered starting material. The best result was approximately 20% yield of **2.250** using triflic acid as the catalyst, but the reaction was irreproducible due to competitive decomposition of the trichloroacetimidate reagent. This reaction also provided complex reaction mixtures, and isolation of pure **2.250** was difficult. Before additional attempts were made to selectively protect the amino alcohol, initial screening was performed to test the N,O-bond cleavage step on the material we already had in hand.

Scheme 2.57

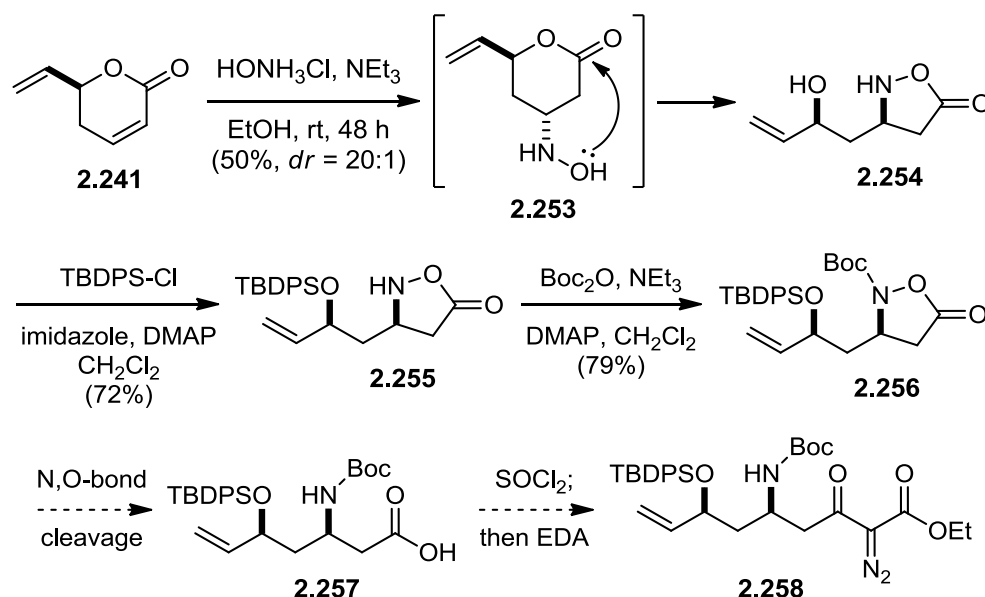


Various standard reaction conditions were screened to cleave the N,O-bond of **2.250** and **2.249**, which included a variety of dissolving metal reductions (Scheme 2.57). Unfortunately, all of the conditions that were investigated illuminated the incompatibility of the diazo functionality with the conditions for N,O-bond cleavage. It is possible that the N,O-bond cleavage would be possible on an earlier intermediate, however, prior to

the installation of the diazo group. Preliminary studies to that end were investigated by Dr. Dan Paull. Unfortunately, we have not been successful at discovering conditions for N,O-bond cleavage of any of the aforementioned synthetic intermediates.

Another intriguing strategy, which takes advantage of the stereoelectronically controlled aza-Michael reaction with lactone **2.241**, involved the use of hydroxyl amine to give the lactone intermediate **2.253**, which underwent a spontaneous intramolecular cyclization to give the isoxazolidinone **2.254** in an unoptimized 50% yield (Scheme 2.58). With this intermediate in hand, refunctionalization of the amino alcohol was accomplished without issue to give the doubly protected **2.256**. No additional attempts were made to advance this strategy; however, it would seem that the N,O-bond cleavage on this substrate would be more trivial than those with the diazo moiety in place. The N-Boc-group should also serve to weaken the N,O-bond and thus make the reduction more facile, however, a discovery made in parallel regarding our initial Hirama cyclization approach excluded the need for a modified synthetic route.

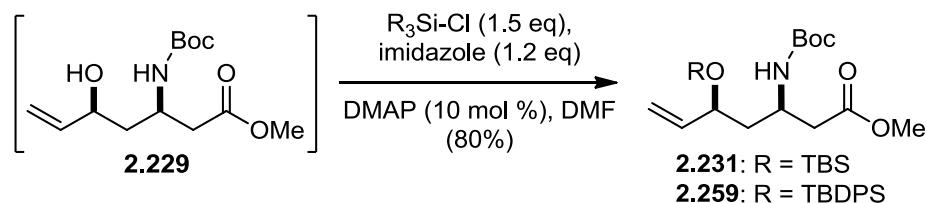
Scheme 2.58



During the efforts made by Dr. Dan Paull to advance material, the silylation of the initial amino alcohol **2.229** was revisited (Scheme 2.59). It was discovered that the silylation of this intermediate could be accomplished in good yield by inverting the stoichiometry of the silyl chloride (1.5 eq) and the imidazole (1.3 eq); previous attempts at this reaction were performed with excess imidazole. Dr. Paull was therefore able to synthesize the TBS-protected compound **2.231** in ~70% yield. It was also discovered that the yields were consistently higher when the TBS-Cl was “preactivated” by stirring with imidazole in DMF for 15-20 min prior to introduction of the alcohol substrate. Elaborating on this discovery, I was able to increase the yield of the silylation further by employing DMAP as a catalyst to furnish the TBDPS-protected amino alcohol **2.259** in 80% yield. The use of DMAP removes the procedural requirement of preactivating the silyl chloride, presumably to pre-form the TBS-imidazole adduct. With the ability to now access the appropriately protected amino alcohol, we were confident that the

impending Claisen condensation would be better behaved than with previous substrates lacking the *O*-protection.

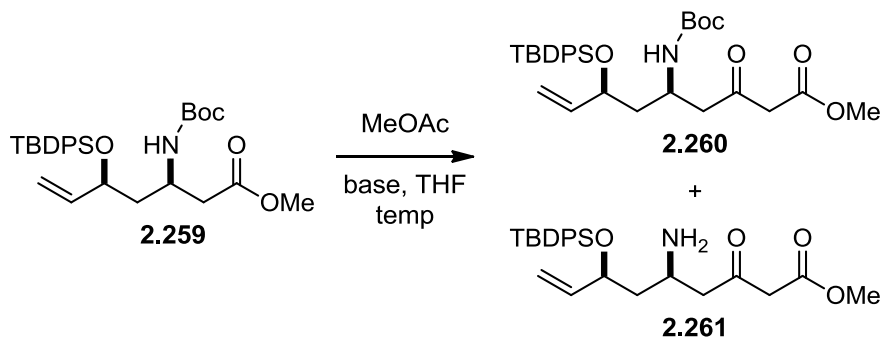
Scheme 2.59



With **2.259** in hand we focused on finding conditions for a high yielding Claisen reaction with a substrate bearing the acidic NH-bond (Table 2.2). This reaction was the focus of a great deal of examination, as were most of the Claisen reactions we encountered. However, we were excited by the fact that the use of the optimized conditions we had used for **2.230** when applied to **2.259** resulted in an increased yield without any initial effort to afford the β -ketoester **2.260** in 60% yield (Table 2.2, Entry 1). We were also able to identify a side reaction that might explain some of the problems we were having in some of our previous Claisen reactions. With all of the trials using LDA as the base, we always isolated the free amino analogue **2.261**. In order to shed light on how we were losing the Boc-protecting under basic conditions, we ran control experiments with both the starting material **2.259** and the isolated product **2.260**. Namely, when these materials were exposed to excess LDA in THF at 0 °C, it became clear that the Boc-group of the starting material was stable. The β -ketoester product **2.260**, however, immediately began generating the amino compound **2.261** corresponding to loss of the Boc-group. Mechanistically it is not clear how this process occurs, but we rationalized that the excess Lewis-acidic lithium counterion might be responsible for the instability of the Boc-group in the product. We therefore screened NaHMDS and in none

of these examples did we observe loss of the Boc-protecting group. After optimization we found that using 13 equivalents of NaHMDS and 10 equivalents of methyl acetate was most effective at generating the enolate of methyl acetate (Table 2.2, Entry 7). Due to dilution requirements in preparing the enolate, the reaction is much more facile when a large excess of base and methyl acetate is used. Applying the optimized conditions, β -ketoester **2.260** was prepared in 75% yield along with 17% recovered starting material.

Table 2.2



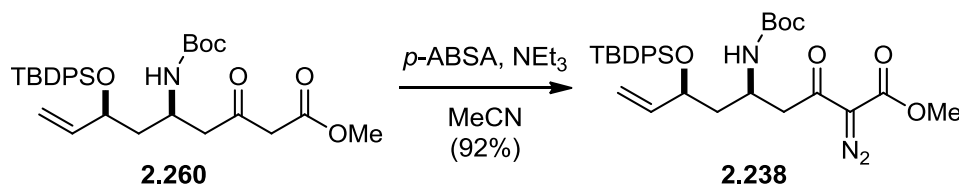
Entry	MeOAc (molar eq)	Base (molar eq)	Temp (°C)	Rxn Time*	Result
1	10	LDA (11)	-78 to 25	1 h; 15 min	60% (full conversion)
2	6	LDA (6)	-78 to 25	1 h; 30 min	35% (full conversion)
3	6	NaHMDS (6)	-78 to 0	1 h; 4 h	~10% conversion
4	6	NaHMDS (7)	-78 to 0	1 h; 4 h	~20% conversion
5	10	NaHMDS (10)	-78 to -10	1 h; 4 h	52% + 41% RSM
6	10	NaHMDS (11)	-78 to -10	1 h; 4 h	60% + 30% RSM
7	10	NaHMDS (13)	-78 to -10	1 h; 6 h	75% + 17% RSM
8	5	NaHMDS (10)	-78 to -10	1 h; 8 h	65% (RSM N/D)

*in each entry, the first time represents how long the reaction was held at the first temperature, and the second time represents how long the reaction was held after warming to the final temperature.

With the problem of the Claisen finally solved, the β -ketoester **2.260** was converted to the diazo- β -ketoester **2.238** in 92% yield using *p*-ABSA and NEt_3 (Scheme 2.60). Compound **2.2.238** was employed in the synthesis of the oxazolidine

cycloaddition precursor **2.240**, and thus the optimized synthesis of this intermediate was finally complete. The synthesis of **2.238** from 2-deoxy-D-ribose (purchased in kilogram quantities for \$0.5/gram) was accomplished in 10 synthetic steps and in 21% overall yield. The synthesis of this compound has subsequently been reproduced multiple times on up to decagram scale, and only requires 4 chromatographic purifications. One way to sum up the efficiency of this sequence is to consider that a 50 g batch of sugar should provide ~45 g of **2.238** in about 2 weeks of lab time (*cf.* Section 2.3 for summary of optimized synthesis).

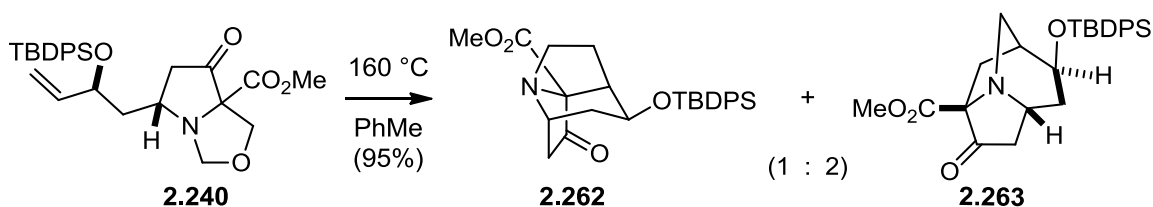
Scheme 2.60



2.2.2.5 Efforts in Developing a Regioselective Cycloaddition Reaction

The work described in the previous section focused on the development of a general synthetic strategy for utilizing 2-deoxy-D-ribose as a starting material toward a synthesis of the stemofoline alkaloids in enantiopure form. With a synthesis of oxazolidine **2.240** in hand, the thermolytic cycloaddition reaction previously employed in the group could now be tested (Scheme 2.61). In the event, thermolysis of **2.240** delivered a mixture (1:2) of regioisomers **2.262** and **2.263** in a combined 95% yield. Unfortunately this ratio fell well short of the what we had hoped for with the C(8)-hydroxyl substituent in place. In fact, it fell short of our previous best ratio of 1:1.

Scheme 2.61

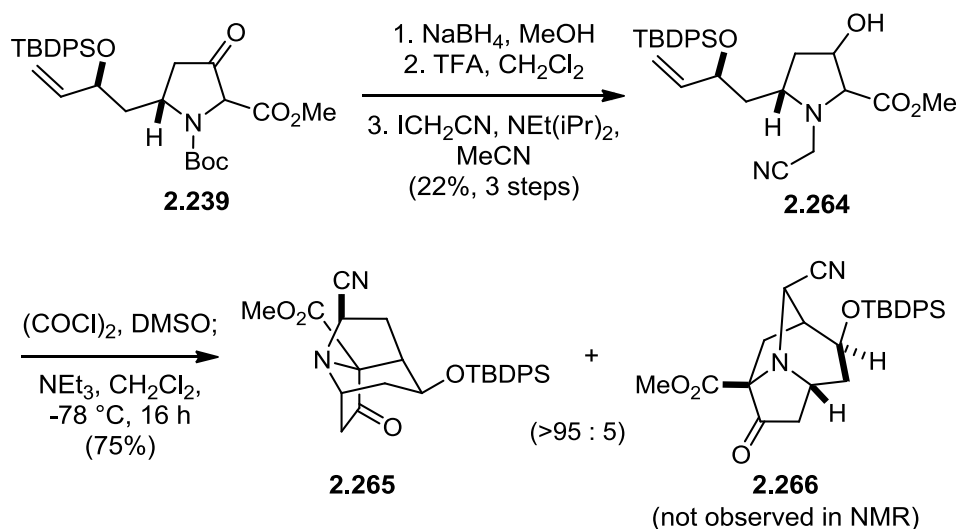


A considerable amount of research thus far had been committed to solving the problem of developing a regioselective intramolecular cycloaddition reaction to construct the stemofoline core using various sterically biased substrates. From the onset, we hoped to identify a steric influence that could be exploited that would favorably affect the cycloaddition outcome; however, it was becoming clear that the effects of sterics alone were not as dramatic as we had hoped. As illustrated by the Swern-mediated cycloaddition reaction, much better regioselectivity was achieved when the electronics of the cycloaddition reaction were adjusted (Scheme 2.18). At this point we became interested in testing the Swern-mediated cycloaddition on a sterically biased system to probe if the effects of sterics plus electronics could be used in conjunction to facilitate a highly selective cycloaddition.

Pyrrolidinone **2.239** was thus diverted to amino nitrile **2.264** by first reducing the ketone with NaBH_4 to deliver a mixture of diastereomeric alcohols (Scheme 2.62). The Boc-protecting group was removed, and the intermediate amine was alkylated with iodoacetonitrile in the presence of Hünig's base. Standard Strecker conditions to construct the aminonitrile resulted in loss of the silyl protecting group in this case. When aminonitrile **2.264** was subjected to Swern conditions, the desired azatricycle **2.265** was obtained in 75% yield as a single regioisomeric cycloadduct. The remarkable selectivity in this example might suggest that the transition state leading to the undesired

cycloadduct **2.266** suffers from additional steric hindrance due to the spatial orientation of the cyano-group and the silyl protected alcohol. In any case, it seems clear that the effects of sterics and electronics are more than just additive as they were first hypothesized to be. It also seems reasonable that perhaps any removable group on the C(5)-position, predisposed towards the C(8)-silanol, might similarly affect the reaction outcome; therefore, we began considering options for replacing the cyano group with something more labile.

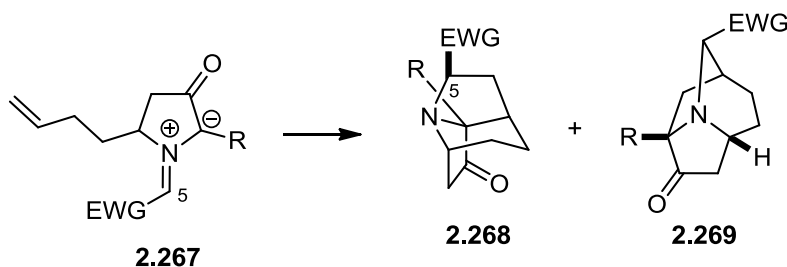
Scheme 2.62



Based on the hypothesis that a group at the C(5)-position, electron withdrawing or otherwise, has a profound effect on the cycloaddition outcome, we next sought to find a group that could be installed prior to cycloaddition that would prove to be more easily removed than the cyano functionality. The main problem with the approach of electronically biasing the cycloaddition reaction has ultimately been the inability to remove the electronic auxiliary from the tricyclic cycloadduct. While decyanation attempts have yet to yield the appropriately functionalized stemofoline core, it would

stand to reason that with further screening this sort of strategy could still be fruitful. It is also of interest to look at other substituents to see if other electron withdrawing groups such as an ester could similarly benefit the cycloaddition (Scheme 2.63). It was also of interest to vary the substitution of the pyrrolidinone ring by varying the R-group of **2.267**.

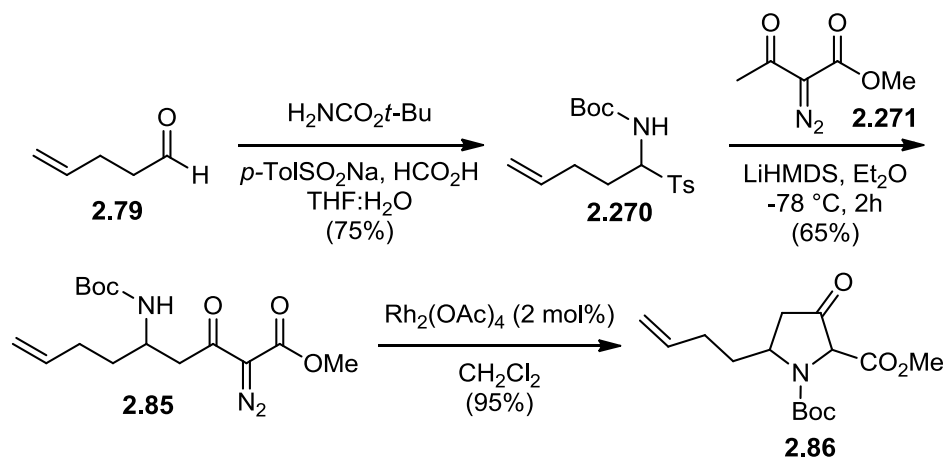
Scheme 2.63



In order to address some of these questions, we returned to the original unsubstituted model system due to the ease in which pyrrolidinone **2.86** can be made to test the aforementioned cycloaddition strategies. With a scalable route to the C(8)-substituted series of compounds, any advancement on the model system could be quickly applied to the more advanced system. A modified synthesis of **2.86** was investigated to facilitate its preparation with good success (Scheme 2.64). Aldehyde **2.79** was first condensed with *t*-butylcarbamate and *p*-toluenesulfinic acid sodium salt to give α -amidosulfone **2.270** in good yield. The product of this reaction crystallized from the reaction mixture and was isolated in pure form by filtration. Next the α -amidosulfone **2.270** was elaborated to diazo- β -ketoester **2.85** by reaction with the lithium enolate of methyl diazomethylacetoacetate (**2.271**). While the titanium enolate of **2.271** was known to react with sulfonimines to give similar tosyl protected Mannich products,⁹⁷ the reaction of the lithium enolate of **2.271** with α -amidosulfones was not known. Accessing racemic **2.86** under these new conditions provided the Boc-protected compound directly

making the overall process more economical. Not only was the length of the synthesis shorted to three steps from the previously required six steps, but the overall yield of the new sequence was increased to 46% from the original 35%. The modified synthesis also benefitted from shorter preparation time and three less chromatographic purifications.

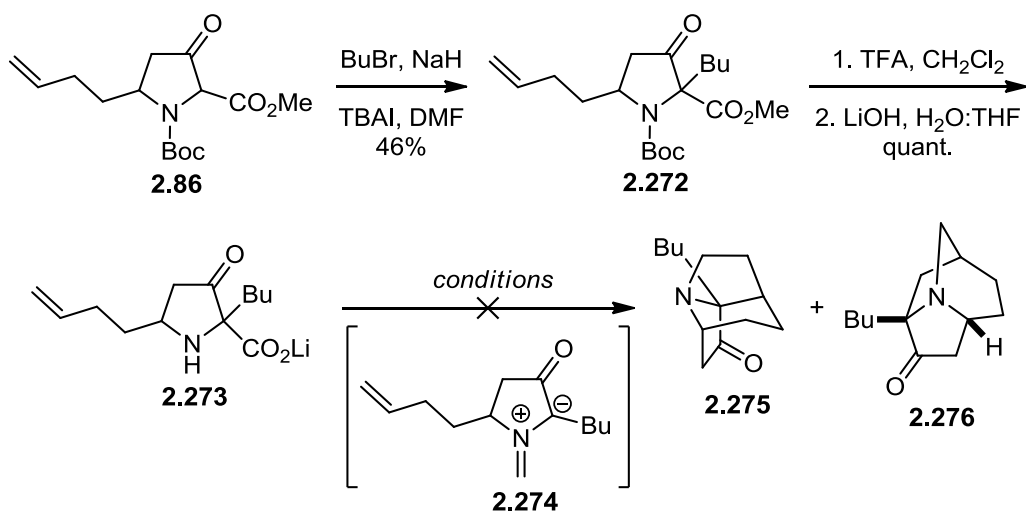
Scheme 2.64



With gram quantities of pyrrolidinone **2.86** in hand, we examined varying the substitution of the azomethine ylide derived directly from this intermediate. We sought to install the butyl side chain present in stemofoline and attempt a decarboxylative reaction to access a potentially more reactive azomethine ylide **2.274** (Scheme 2.65). β -Ketoester **2.86** was first treated with *n*-butylbromide in the presence of sodium hydride/TBAI, and the *C*-alkylated product **2.272** was obtained in 46% yield; variable amounts of *O*-alkylation were also observed. The carbamate moiety was then removed with TFA, and the methyl ester was saponified with $\text{LiOH}/\text{H}_2\text{O}$ to give aminocarboxylate **2.273** in virtually quantitative overall yield. The carboxylate salt was then used without purification in a number of cycloaddition attempts including: thermolysis with paraformaldehyde with no additional additives and with various amounts of *p*-TsOH.

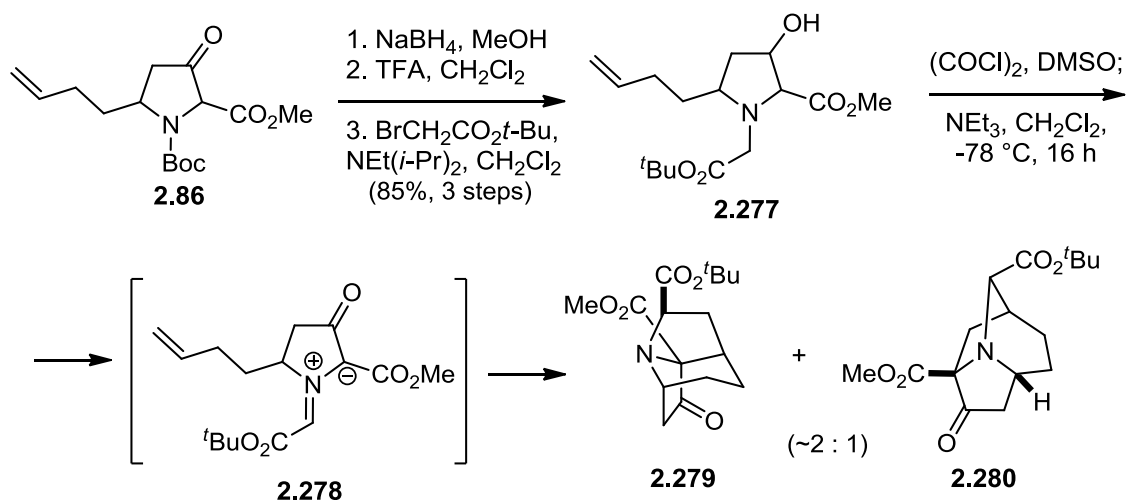
The only observable product in any case was simply the decarboxylated product with no observable cycloadduct(s).

Scheme 2.65



We then inquired whether an ester group in the azomethine ylide might lead to high regioselectivity in the dipolar cycloaddition with the Swern-like azomethine ylide formation (Scheme 2.66). Accordingly, we reduced the β -ketoester **2.86** with NaBH_4 , removed the Boc-protecting group with TFA , and N-alkylated the intermediate amine with *t*-butyl bromoacetate to give aminoester **2.277** in 85% over three steps.

Scheme 2.66



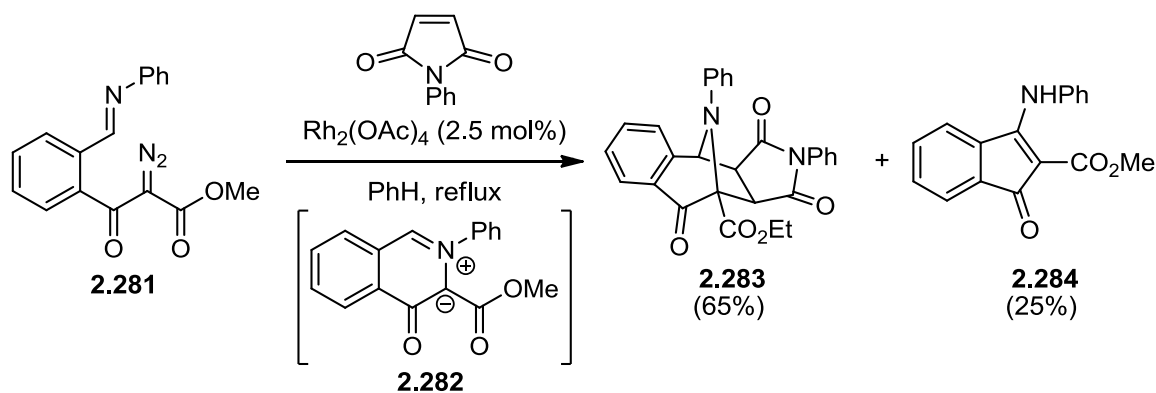
Aminoester **2.277** was then subjected to the established azomethine ylide formation under Swern oxidation conditions and, unfortunately, proved to be much less reactive than the comparable cyanated-analogue **2.102** (Scheme 2.66). The starting material was consumed in the reaction, but gave low conversion to the two cycloadducts **2.279** and **2.280**. The complexity of the reaction mixture made the ratio of the cycloadducts hard to elucidate, but was tentatively assigned as ~2:1 of **2.279**:**2.280** based on the ^1H NMR of the reaction mixture. While the full product distribution of this particular reaction is still not totally clear, the presence of both regioisomeric cycloadducts was confirmed, and it seems that the reaction undergo complete conversion to azomethine ylide under the established conditions. This would suggest that future trials of this reaction may require elevated temperatures if, for example, aziridine intermediates are forming from the azomethine ylide before it can react in the desired cycloaddition.

Despite the low yield of cycloadducts, we were encouraged in that the reaction involving an azomethine ylide generated from **2.277** worked to some extent. This was

an important breakthrough because there are a number of procedures for radical decarboxylation in the literature, a class of reactions that has shown great scope in organic synthesis. The inherent regioisomeric ratio was not as high with **2.278** as the example with the cyano-substitution **2.102**, a fact that may indicate the importance of electronics as a regiochemical control element since the *t*-butyl ester is considerably more hindered but less electronegative than the cyano group. Despite the low conversion to cycloadducts and the lower than anticipated regioisomeric ratio, we felt confident that such an azomethine ylide would provide much higher selectivity when applied to the C(8)-substituted series of compounds, and thus we turned our attention to this series of compounds.

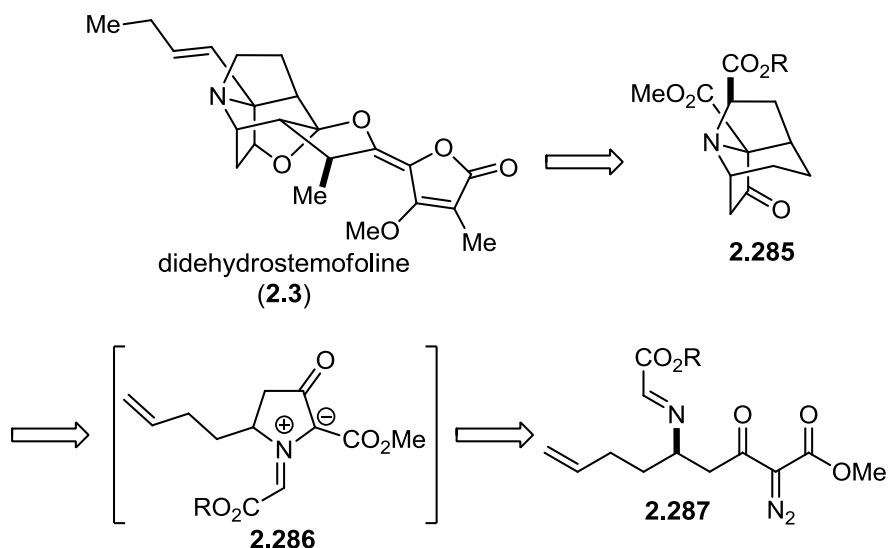
We became interested forming an azomethine ylide related to **2.278** in a potentially more facile way. Cognizant of the fact that metallocarbenoids react with imines to form azomethine ylides,^{127, 128} we became interested in applying such a reaction to our own system. After a thorough literature search, however, we could only find one report of exploiting this reactivity in an intramolecular sense. Padwa had shown that the azomethine ylide **2.282** could be formed from an intramolecular reaction of an imine with a tethered diazo- β -ketoester **2.281** catalyzed by Rh₂(OAc)₄ (Scheme 2.67).¹²⁷ The azomethine ylide formed from this reaction was utilized in an intermolecular 1,3-dipolar cycloaddition with N-phenylmaleidimide to give cycloadduct **2.283** in 65% yield. Padwa also utilized this 1,3-dipole cascade reaction on the comparable oxime (rather than imine) of **2.281** with similar results in forming the hydroxylamine variant of **2.283**, but only applied this procedure to a limited set of cycloaddition examples. No attempt has yet been made to apply this chemistry in the realm of natural product synthesis, thus we were excited by the possibility of applying this novel methodology to our own system.

Scheme 2.67



Our adaptation of Padwa's 1,3-dipole cascade reaction would be considerably more aggressive, in that we were not only aiming to form the azomethine ylide **2.286** in an intramolecular sense using the dipole cascade reaction, but a tethered olefin would set up a significantly more demanding intramolecular dipolar cycloaddition (Scheme 2.68). Another significant modification is that the imine in our system would be exocyclic and used to form a 5-membered cyclic ylide, whereas in the Padwa example, the imine was endocyclic. Our envisioned all-intramolecular cascade reaction would provide the stemofoline core in one single operation starting from the acyclic diazo-β-ketoester **2.287**, thus completely bypassing our usual pyrrolidinone intermediate. Based on the aforementioned Swern-mediated cycloaddition that was used to access a similar carboxylated azomethine ylide **2.286**, we were confident that if we could form the azomethine ylide under these conditions a favorable regioselectivity would result to give the carboxylated stemofoline core **2.285**.

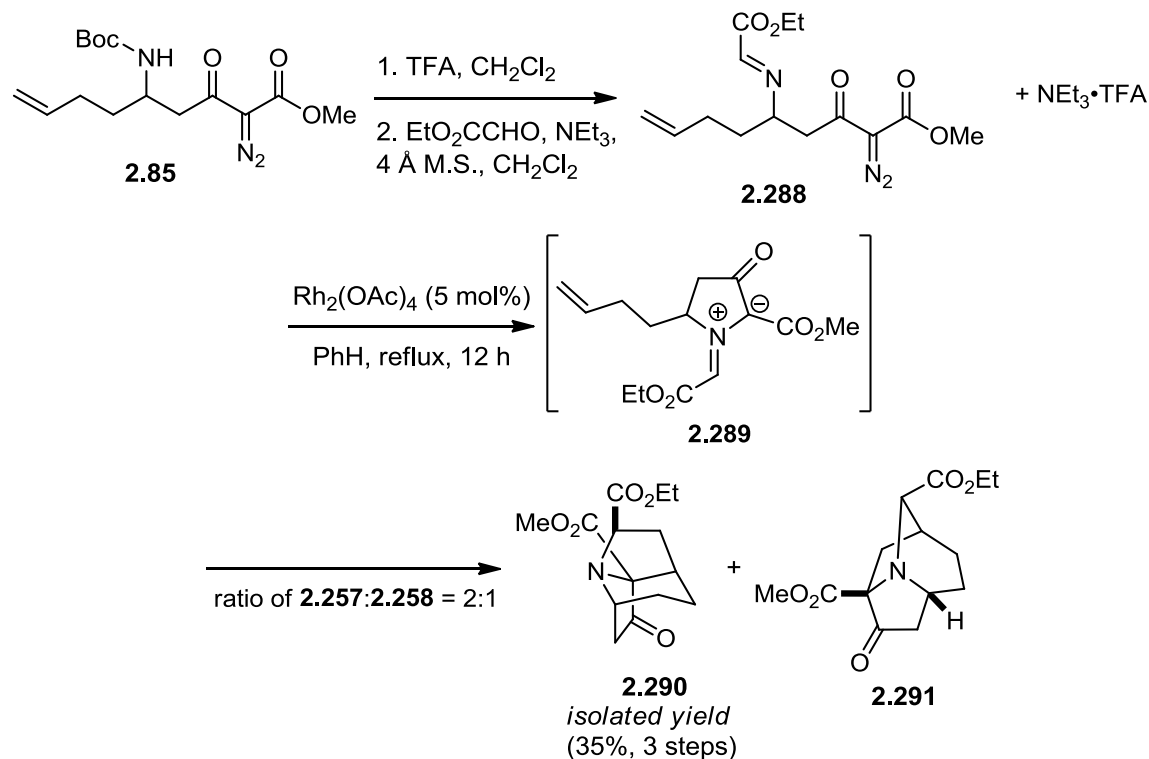
Scheme 2.68



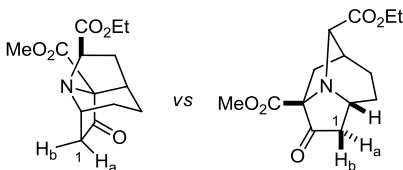
In order to assess the feasibility of this new route, we removed the Boc-protecting group from the diazo- β -ketoester **2.85** with TFA to give the corresponding amine-TFA salt (Scheme 2.69). We next formed an imine with ethyl glyoxylate in the presence of NEt_3 and 4 Å MS to provide diazoimine **2.288**. Analysis of the crude material revealed only the diazoimine and an equimolar amount of $\text{NEt}_3 \cdot \text{TFA}$. Due to the fact that $\text{NEt}_3 \cdot \text{TFA}$ is an oil, it was not possible to remove the salt by precipitation. Since we were operating under the assumption that the imine was moisture sensitive, we decided to run our initial cycloaddition experiment with the salt contaminant in order to establish the basic reactivity of the targeted cycloaddition reaction. We were excited to find that treatment of **2.288** with a catalytic amount of $\text{Rh}_2(\text{OAc})_4$ in refluxing benzene provided a mixture (2:1) of the carboxylated cycloadducts **2.290** and **2.291** in approximately 53% combined yield over the three step sequence. The isolated yield of the desired cycloadduct **2.290** was 35% from **2.288**, which was very encouraging considering that

this sequence was still far from optimized. Most importantly, a desirable regioselectivity was obtained, which we anticipated to only improve when applied to the real system.^{xxiv}

Scheme 2.69



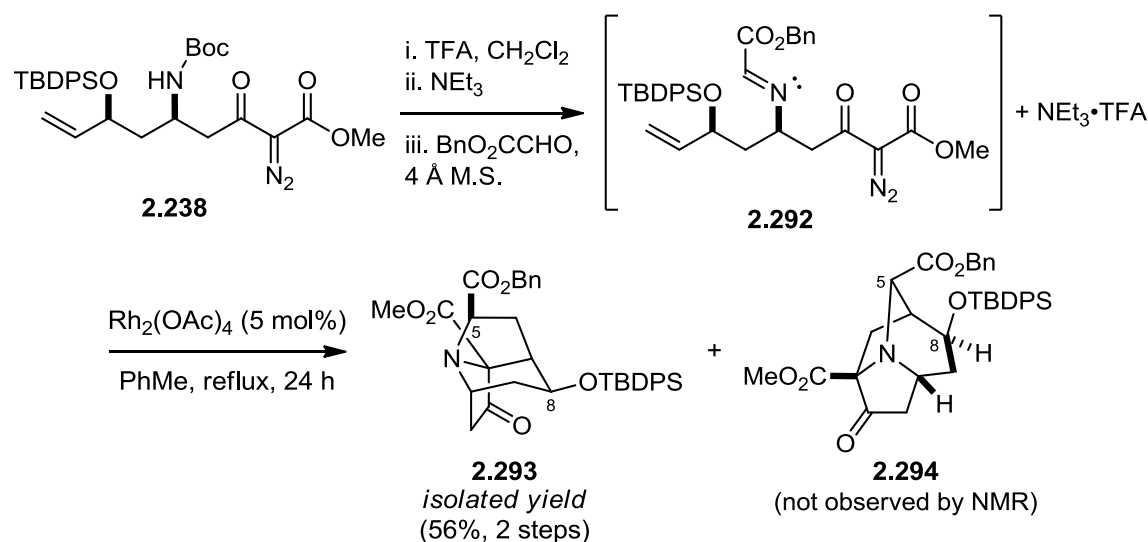
^{xxiv} It should be noted here that the two different regioisomers are easy to identify in the crude ¹H NMR spectrum by identification of the C1-*endo* protons (labeled “H_a”). These protons show up as distinct doublets in the ¹H NMR spectrum and give very diagnostic *J*-coupling values. The desired tricycle always gives a doublet with a *J*-coupling of 17.6 Hz, and the undesired has a *J*-coupling of 15.6 Hz. These values are consistent with every set of regioisomeric cycloadducts that have been prepared in the group to date.



With an efficient synthetic route to **2.238** already established, the application of our new cascade cycloaddition reaction to the real system could be quickly explored (Scheme 2.70). The nitrogen atom of **2.238** was refunctionalized by removal of the Boc-protecting group, and condensation of the intermediate amine with benzyl glyoxylate^{xxv} gave crude diazo imine **2.292**. Analysis of the crude imine by ¹H NMR spectroscopy, after a filtration through Celite, revealed quantitative conversion to the desired imine along with an equimolar amount of NEt₃•TFA. Since filtration of NEt₃•TFA was not possible, we again carried the mixture to the cycloaddition step. The crude diazoimine **2.292** was thus treated with a catalytic amount of Rh₂(OAc)₄ in refluxing toluene, and the desired tricycle **2.293** was obtained in 56% isolated yield as the only observable regioisomer over the three-step/two-pot sequence. That none of the undesired tricycle was observed in the NMR spectrum of the crude reaction mixture, is undoubtedly a testament to the multiplicative effect of combining the C(5)-electron withdrawing group with the bulky C(8)-OTBDPS group.

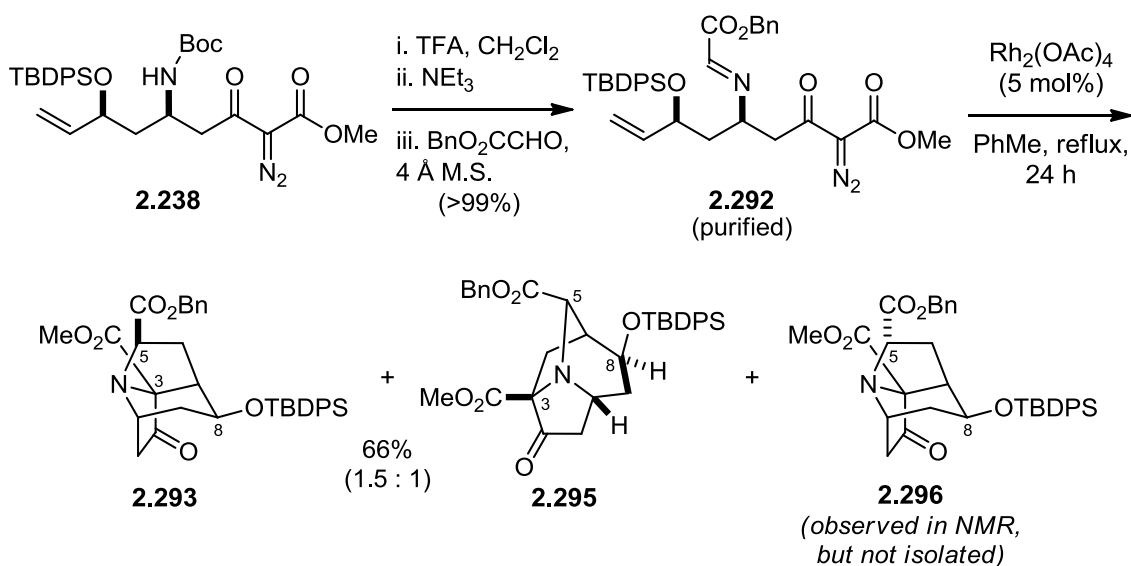
^{xxv} Preparation of benzyl glyoxylate on large scale using established procedures had proven difficult and expensive. Thus we developed a procedure which essentially solves the problem of the large scale preparation of high boiling glyoxylates by reaction of glyoxylic acid (2 eq) with benzyl alcohol (1 eq) in refluxing toluene under Dean-Stark conditions for ~24 h. Excess glyoxylic acid serves as the acid catalyst for the esterification and is easily removed by acid/base extraction of the reaction mixture to give clean benzyl glyoxylate directly.

Scheme 2.70



In order to optimize this reaction, we wanted to see if removing the NEt₃•TFA impurity from the crude diazo imine would increase the overall yield. The crude diazoimine was then passed through an oven-dried plug of basic alumina and washed with anhydrous dichloromethane. Attempts to perform this operation as a vacuum filtration led to significant loss of the imine, presumably the result of hydrolysis. The best results were obtained by performing the filtration under an atmosphere of nitrogen gas, and the pure imine **2.292** was obtained in quantitative yield (Scheme 2.71). Upon subjecting the purified diazoimine to the cycloaddition conditions, a slight increased conversion was observed; however, the regioisomeric ratio had greatly deteriorated. Analysis of the ¹H NMR spectrum of the crude reaction mixture suggested a regioisomeric ratio of ~1.5:1 of **2.293** relative to **2.295**, which were isolated in a combined 66% yield.

Scheme 2.71



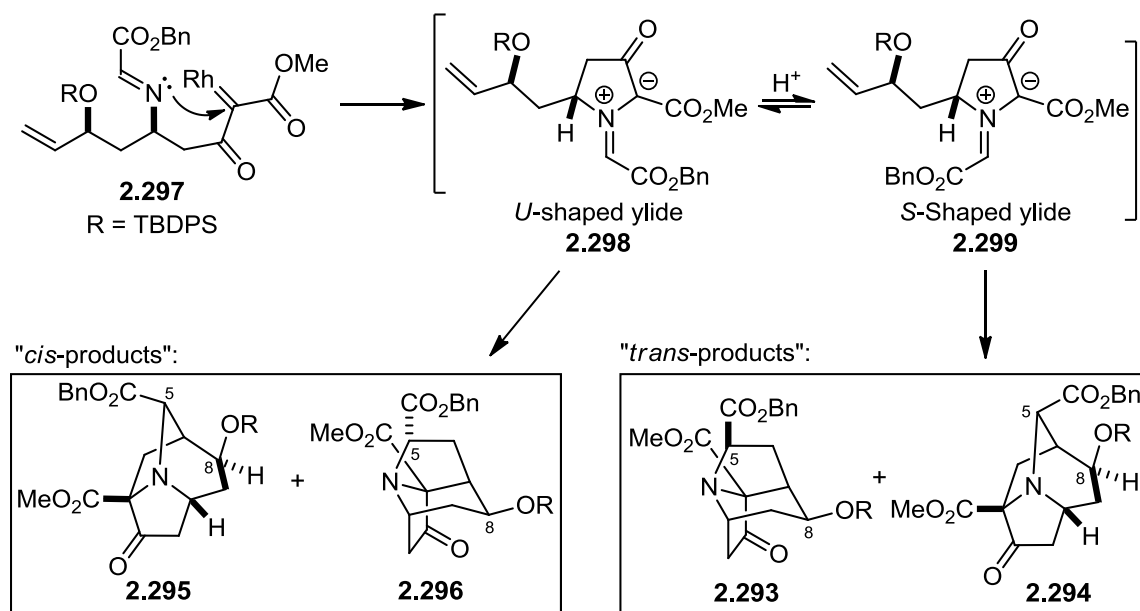
The stereochemistry at C(5) of the undesired regioisomer also merits comment. In the case of the cyano-substituted system **2.102** (Scheme 2.18) the *anti*-stereochemistry, relative to the C(3)-ester and the C(5)-cyano groups, was always observed in the products. This is not surprising because the intermediate azomethine ylide should prefer the *S*-shaped geometry that would lead to the *anti*-orientation of the two ester groups. The *S*-shaped azomethine ylide would also correspond to the dipole minimized conformation making it electronically favorable as well. In the cycloaddition example above (Scheme 2.71), however, it is believed that the stereochemistry of **2.295** is actually one in which the C(3)- and C(5)-ester groups are *cis* relative to one another. While this assignment is still tentative, this is believed to be the case for a variety of reasons, including the fact chemical shift of the C(5)-proton was ~0.5 ppm upfield from typical values for these types of cycloadducts. A similar shift in values has been observed with compound **2.102** (Scheme 2.18), when the epimerized product was obtained in an attempted silylation reaction in the presence of excess sodium hydride. Also, as is

typically observed, the undesired regioisomers in all the cycloaddition reactions to date have been considerably less polar than the desired regioisomer (by TLC). In this case, however, **2.293** and **2.295** had virtually the same R_f by TLC. The relative increase in polarity of **2.295** might be a result of the 3,5-*cis*-orientation due to the additive nature of the both of the esters dipoles, an orientation that is likely lead to higher overall polarity of the molecule. Also of note was the presence of ~10% of a third cycloadduct, the ^1H NMR spectrum of which looked identical to **2.293** except for the chemical shift of the C(5)-proton that showed up ~0.5 ppm upfield, which seems to be a phenomenon indicative of epimerization of the C(5)-stereocenter. Thus the third cycloadduct was assigned to be epimer **2.296**.

While the result with the purified diazo imine (Scheme 2.71) is still somewhat puzzling, it has become clear that the presence of a proton source such as $\text{NEt}_3 \cdot \text{TFA}$ is essential to steering the reaction toward the desired cycloadduct. In order to explain this observation, an analysis of the intermediate azomethine ylide geometry is necessary (Scheme 2.72). It is widely accepted that 1,3-disubstituted azomethine ylides can react out of two discrete conformations, being the *cis*- and *trans*-ylide geometries (or the so called *U*- or *S*-shaped geometries). With respect to our system, the initial trisubstituted ylide that should form from the imine reacting with the appended carbenoid **2.297** is the ylide where both the ester groups are oriented *cis* to one another (**2.298**, Scheme 2.75). If this intermediate has enough energy to undergo the intramolecular cycloaddition reaction, then the regioisomeric product obtained would be those where the esters at the C(3)- and C(5)-positions are similarly in a *cis*-orientation (**2.295** and **2.296**). Presumably, in the case with the purified imine (Scheme 2.71), this *U*-shaped ylide is considerably more populated than in the initial example with the $\text{NEt}_3 \cdot \text{TFA}$ additive (Scheme 2.70). The only significant difference between the reaction with the crude and purified imine is the

presence of the $\text{NEt}_3 \cdot \text{TFA}$ salt. It would, therefore, seem that the presence of a proton source in the cycloaddition reaction leads to a rapid equilibration of the ylide geometries allowing the intermediate ylides to funnel to the more stable *S*-shaped ylide (**2.299**). The product of reaction out of the *S*-shaped ylide geometry would therefore be cycloadducts **2.293** and **2.294**. The formation of **2.294** has yet to be confirmed in any cycloaddition reaction, however, presumably not forming because of the severe interaction between the C(5)-ester and C(8)-silanol. The undesired cycloadduct **2.295** does not suffer from this type of steric disadvantage, which would explain why more of this isomer forms when reacting out of the *U*-shaped geometry.

Scheme 2.72



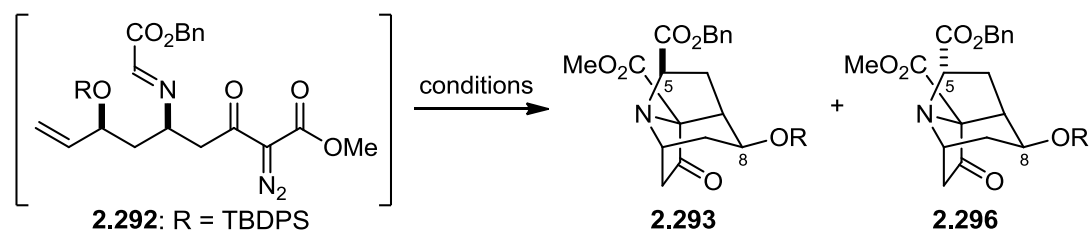
Whatever the operative principles of the new cycloaddition reaction truly are, it is clear that a proton source is necessary in the cycloaddition reaction in order to obtain high levels of regioselectivity. With this fact determined, a series of experiments were

devised to probe the effect of further raising the reaction temperature in order to increase the yield of the cycloaddition reaction. Summarized in Table 2.3 are the pertinent results to describe what has thus far been learned about the key dipole cascade cycloaddition. When the crude imine was heated at 150 °C in the microwave over the course of 2 h (Table 2.3, Entry 3), a 74% yield of a mixture (1.5:1) of cycloadducts **2.293** and its C(5)-epimer **2.296** was obtained. Interestingly none of the undesired cycloadduct was observed in this reaction. This may suggest that the undesired C(5)-epimer **2.296** may be forming in some cases by epimerization after the cycloaddition event rather than as a result of the *U*-shaped ylide. This hypothesis was confirmed by reducing the reaction time in the microwave to 30 min (Table 1, Entry 4), where only trace amounts of the C5-epimer **2.296** were observed in the NMR spectrum. While the isolated yield of **2.293** was comparable to that of the initial cycloaddition reaction, it is noteworthy that the cycloaddition is virtually complete after only 30 minutes whereas conventional heating in refluxing toluene requires nearly 24 hours.

Further improvements to the key cycloaddition reaction came from increasing the reaction temperature from refluxing toluene (110 °C) to refluxing xylenes (~135 °C). The increase in reaction temperature provided the desired cycloadduct in 65% yield from the carbamate **2.238** along with variable amounts of the C(5)-epimer **2.296**. Also the catalyst loading could be lowered to 2 mol % of the dirhodium catalyst (corresponding to an effective 4 mol % of rhodium) without loss in yield. A number of reactions were performed at 1 mol % dirhodium, and in some cases the yield was 65%, but the reaction was less reproducible at this catalyst loading. One final experiment that deserves consideration, is the example catalyzed by Cu(TBS)₂ (TBS = *t*-butyl salicylimine), which provided a comparable yield to that in Entry 6. This experiment, however, was only performed once and therefore the reproducibility is not certain. The advantage copper

would provide as a catalyst is that it is considerably cheaper than rhodium, and therefore should be considered as a possible catalyst for future scale up efforts.

Table 2.3



Entry	Conditions	Result (Yield)
1	Rh ₂ (OAc) ₄ (5 mol%), NEt ₃ •TFA (1 eq), PhMe, reflux, 24 h	2.293 (56%)
2	Rh ₂ (OAc) ₄ (5 mol%), PhMe, reflux, 24 h	2.293 (40%) + 2.296 (26%) + 2.263
3	Rh ₂ (OAc) ₄ (5 mol%), NEt ₃ •TFA (1 eq), PhMe, microwave, 150 °C, 2 h	2.293 (44%) + 2.296 (30%)
4	Rh ₂ (OAc) ₄ (5 mol%), NEt ₃ •TFA (1 eq), PhMe, microwave, 150 °C, 30 min	2.293 (57%) + 2.296 (trace)
5	Rh ₂ (OAc) ₄ (5 mol%), NEt ₃ •TFA (1 eq), xylenes, reflux, 24 h	2.293 (65%) + 2.296 (5-10%)
6*	Rh ₂ (OAc) ₄ (2 mol%), NEt ₃ •TFA (1 eq), xylenes, reflux, 24 h	2.293 (65%) + 2.296 (N.D.)
7	Cu(TBS) ₂ (4 mol%), NEt ₃ •TFA (1 eq), xylenes, reflux, 24 h	2.293 (67%) + 2.296 (N.D.)

**This is currently the procedure being used to prepare material.*

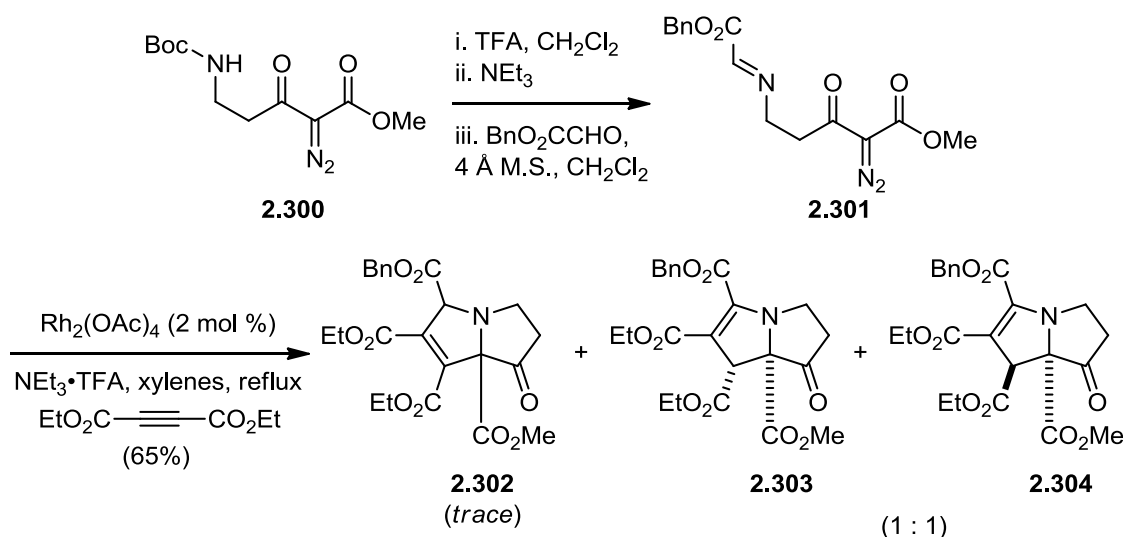
The newly developed cycloaddition reaction was a huge victory for our overall research efforts on stemofoline due, not only to the inherent regioselectivity of the cycloaddition, but due to the preceding steps of the synthesis that provide a scalable approach to this key step. The synthesis of azatricycle **2.293** is now 13 synthetic steps and 14% overall yield. Furthermore, the process for the preparation of this tricyclic core

has been optimized with practicality in mind, and the route only requires six chromatography steps, and few steps are considered air or moisture sensitive. The previous synthesis of the C(9)-substituted azatricycle **2.171** by comparison was 15 total steps and provided the stemofoline core in ~7% overall yield. The previous approach was also far less operationally efficient since it required 11 chromatography steps, a number of which were used to separate closely eluting diastereomers. Furthermore, the previous generation utilized two stoichiometric chiral auxiliaries to handle the challenge of stereochemical control, which further added to the cost of the synthesis. Regardless of our ability to access **2.293** on scale, however, we still needed to prove that a radical decarboxylation was indeed possible to provide the appropriately functionalized natural product core.

With the practicalities of the overall synthesis aside, the new dipole cascade cycloaddition reaction is also unique in that only the Padwa precedent discussed earlier bears any resemblance to this type of reactivity. Due to the novelty of this cycloaddition reaction, we became interested in exploring a bimolecular variant to probe the possibility of applying this reaction in a more general sense (Scheme 2.73). To test this possibility, diazocarbamate **2.300** was treated with TFA to effect Boc-deprotection; subsequent imine formation with NEt₃ and benzyl glyoxylate provided diazoimine **2.301** along with an equimolar amount of NEt₃•TFA. This mixture was then subjected to the standard cycloaddition conditions in the presence of the dipolarophile ethyl acetylenedicarboxylate and a mixture (~1:1) of cycloadducts **2.303** and **2.304** was isolated in 65% yield. It is tentatively believed that the products isolated were the product of olefin isomerization to the more stable vinylogous carbamate after the cycloaddition reaction. This conclusion was made based on a combination NMR, LCMS, and TLC analyses. With respect to the TLC experiment, we were interested in trying to form the HCl-salts of the basic amino

cycloadducts, however upon exposure of the product mixture to 2 M HCl/MeOH, the TLC (SiO₂, 1:1 Hex:EtOAc) revealed no change in R_f. If the products were the amino cycloadducts then they would have protonated, and not eluted up the TLC plate; thus we assumed the product was likely the isomerized vinylogous carbamates **2.303** and **2.304** which are not basic. Based on this presumed isomerization, it is likely that the 1:1 ratio does not represent the actual diastereoselectivity of the cycloaddition. Despite the fact that this combination of substrates was not the most synthetically interesting, it did establish the viability of a potential general method.

Scheme 2.73

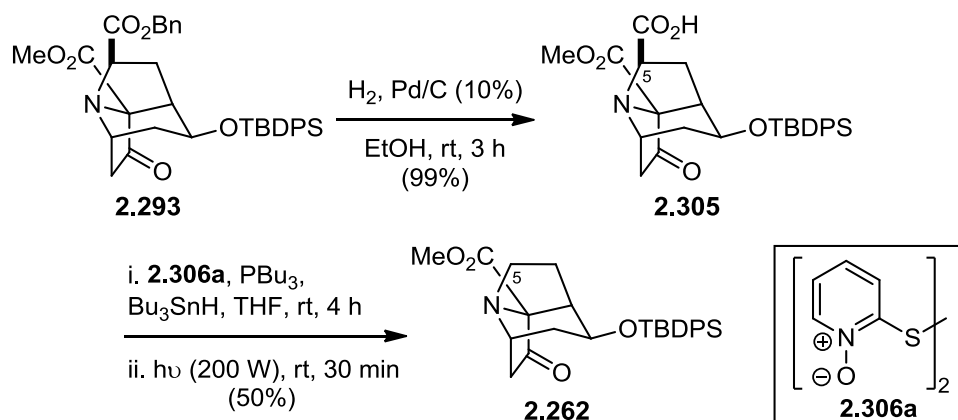


2.2.2.6 Decarboxylation of the Azatricyclic Core

With a reliable way to make the fully functionalized stemofoline core now at our disposal, the next critical challenge was to prove the feasibility of removing the ester at C(5) of tricycle **2.293**. In order to explore various possibilities, the benzyl ester was subjected to hydrogenolysis with Pd/C to furnish amino acid **2.305** in quantitative yield

(Scheme 2.74). With acid **2.305** in hand, we next screened a variety of different conditions to effect a radical decarboxylation or decarbonylation. A few different methods for synthesizing a Barton ester were screened, and on small scale reactions, the best procedure proved to be the reaction of tributylphosphine with disulfide **2.306a** in the presence of the **2.305**. When Barton ester formation was complete, the reaction was irradiated with a Tungsten filament light bulb (200 W) under various conditions. It was found that the decarboxylated product was unstable at high temperatures, thus precluding the use of standard AIBN initiated protocols. When the reaction temperature was strictly controlled and maintained at room temperature, irradiation for 30 min was sufficient to consume the Barton ester. This reaction mixture, however, was very complex and isolation of **2.262** proved difficult. The formation of **2.262** was confirmed by comparison with an authentic sample by TLC (formed from the thermolytic cycloadditions, Scheme 2.61), by analysis of the crude reaction mixture by LCMS, and comparison of the purified ^1H NMR to the previously acquired spectra. Attempted purification of this mixture did provide a 50% yield of the cycloadduct; however, the isolated compound was contaminated by either tributylphosphine oxide or a tributylstannane by-product. These experiments were performed on a small scale, and a larger scale experiment may yield better results. Furthermore, the use of PBU_3 to form the Barton ester was probably not optimal due to necessity to remove the excess by-products; thus another set of Barton ester formation conditions will probably prove more ideal. These preliminary experiments, however, did unequivocally confirm that the desired decarboxylation was indeed possible.

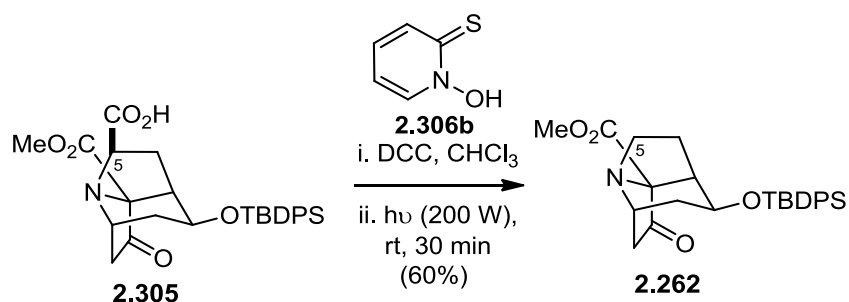
Scheme 2.74



A more recent advancement in the field of radical decarboxylations came from an account by the Williams group, which reported two very important breakthroughs with the Barton reaction.¹²⁹ First, Williams established that chloroform is a competent and general hydrogen atom donor for use in the Barton decarboxylation reaction when used as the reaction solvent. Furthermore, since chloroform was used as the solvent, they were able to perform a one-pot Barton ester formation/radical decarboxylation, essentially rendering the Barton reaction a one step process from the carboxylic acid. This procedure was reported very recently, but undoubtedly due to the reduced “cost, smell, and toxicity” of this procedure it will likely become standard conditions for this type of reaction in the future. Remarkably we had been screening conditions to accomplish the exact feat in using chloroform as a hydrogen atom donor when this paper was published. We therefore applied the reported conditions to our system by first forming the Barton ester from amino acid **2.305** with pyridine thione **2.306b** and DCC in chloroform. Upon complete consumption of the starting material, irradiation of reaction with a tungsten filament light bulb (200 W) for ~30 min at room temperature provided the decarboxylated tricycle **2.262** in ~60% yield. Since this decarboxylation was performed

on a small scale, this yield is likely to improve in future work. Compound **2.262** will likely prove an important compound going forward in the total synthesis; although it is also possible that the decarboxylation reaction could be performed on a number of different synthetic intermediates. The point at which this operation will be synthetically optimal has yet to be decided; as such, we next turned our attention to the construction of the lactone moiety without further optimizing this transformation.

Scheme 2.75

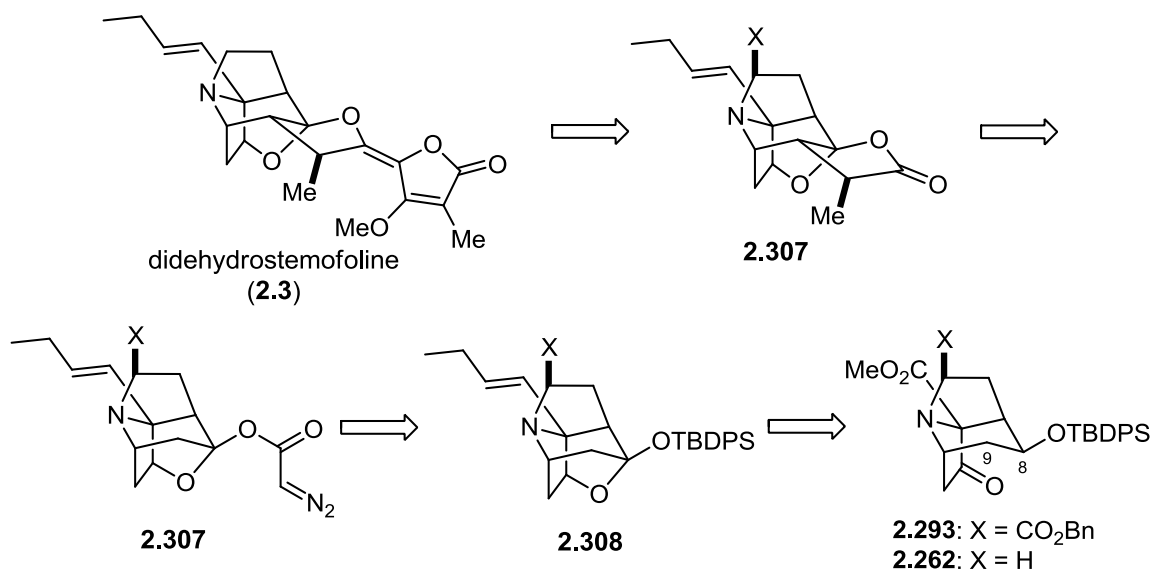


2.2.2.7 Efforts towards the Application of a Novel CH-Insertion Reaction to Construct the Remainder of the Natural Product Core

The next chapter in our efforts to access the final target didehydrostemofoline (**2.3**) now focused on the construction of the targeted lactone ring. At this stage, we wanted to explore the feasibility of a unique and ambitious endgame to finalize our overall approach. In particular, we targeted the construction of the lactone of type **2.307** via a novel dirhodium catalyzed regioselective CH-insertion of diazoacetate **2.307**. While this type of transformation is known, it has never been applied to a system as complex as the one at hand. The key diazoacetate **2.307** would be derived from lactol **2.308**, which would be derived from the cycloadduct **2.293** using a remote

functionalization to oxidize the C(8)-position and a Julia-Kocienski olefination to install the C(3)-butenyl side chain.

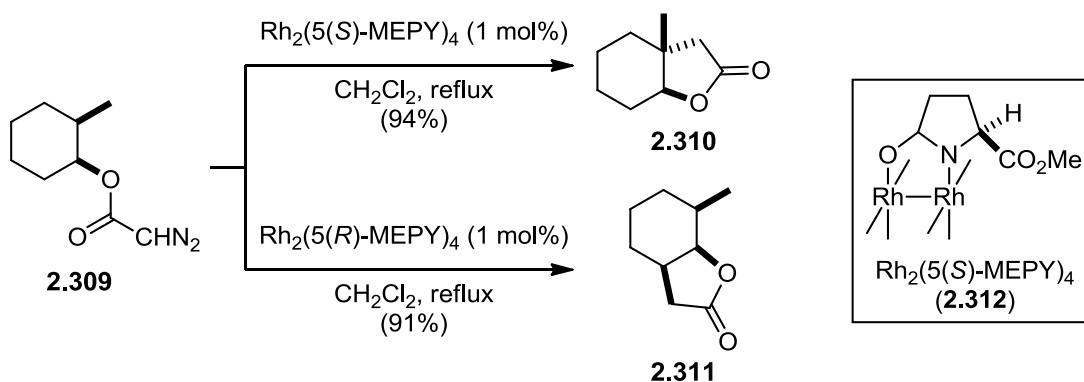
Scheme 2.76



The work of the Doyle group has established the underlying reactivity for our proposed CH-insertion step. They were able to control the regioselection of intramolecular CH-insertion reactions to prepare butyrolactones with high diastereoselectivity. In one relevant example, diazoacetate **2.309** could be diverted to two different products based on the chirality of the rhodium catalyst (Scheme 2.77). Treating **2.309** with dirhodium(II) tetrakis[methyl 2-oxopyrrolidine-5(*S*)-carboxylate] or Rh₂(5(*S*)-MEPY)₄ (**2.312**) resulted in a CH-insertion reaction with the tertiary hydrogen to give lactone **2.310** in 94% yield. When using the opposite enantiomer of the catalyst Rh₂(5(*S*)-MEPY)₄, however, diazoacetate **2.309** provided the product of CH-insertion with the opposite secondary hydrogen atom to give **2.311** in 91% yield. Doyle's work on this class of reactions, has clearly established that these insertion reactions are always

selective for the equatorial hydrogens. The established reactivity we feel bodes well for our envisioned application of this chemistry to stemofoline (Scheme 2.79). The diazoacetate **2.307** we are looking to access has a number of unknowns built into it. To our knowledge, there are no reported monosubstituted diazoacetates as part of a molecule bearing a basic nitrogen nor are there examples of diazoacetates of hemiacetals in the literature. Both of these factors may present a challenge because the diazo hydrogen is considerably acidic, and can undergo deprotonation with amine bases.

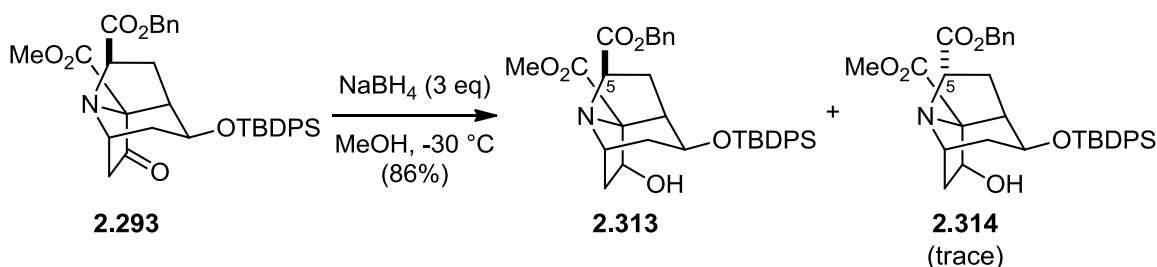
Scheme 2.77. Doyle – Catalyst Controlled Stereoselective CH-Insertion of Diazoacetates



With the CH-insertion reaction in mind, we turned our attention first to the functionalization of the C(8)-position while maintaining the C(5)-ester group for the time being. Since **2.293** can conceivably be utilized in a number of different ways, we wanted to establish proof of principle for the proposed CH-insertion using it directly. To that end, ketone **2.239** was stereoselectively reduced to give the alcohol **2.313** in 86% yield (Scheme 2.78). This type reduction was preceded in the group, and has been shown to be entirely stereoselective. Unfortunately, the C(5)-stereocenter underwent some epimerization under standard reduction conditions. With 1.2 eq NaBH_4 , there was as

much as 17% of the epimer **2.314** isolated, which we rationalized was being produced from the small amounts of sodium methoxide generated during this reaction. We therefore attempted to use 2-propanol as the solvent in the hope that a more sterically hindered alkoxide might be slower to effect the epimerization; however, the epimerization was actually more facile. We finally reasoned that if we increased the equivalents of borohydride relative to the substrate that the reduction would be more rapid and thus give the epimerization less time to occur. This tactic worked quite well to provide the desired alcohol **2.313** in 89% yield with only trace amounts of the C(5)-epimer.

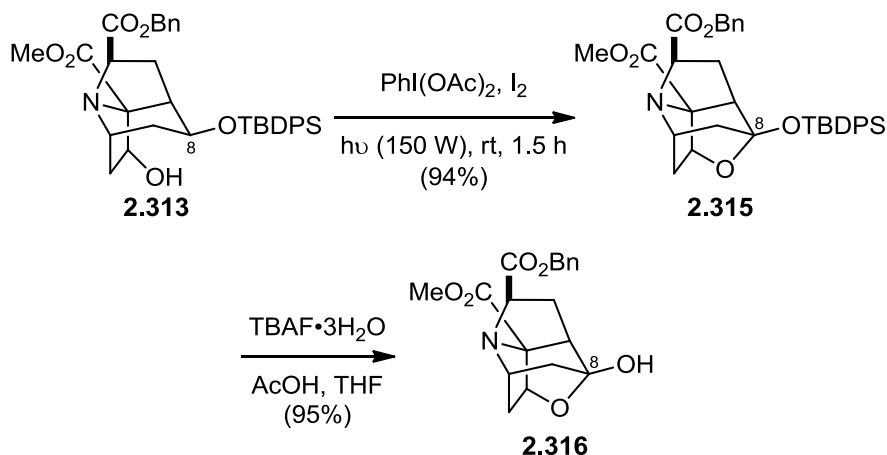
Scheme 2.78



We next applied a Suarez remote radical functionalization that had proved successful in the past for functionalizing the C(8)-position (Scheme 2.79). The difference between this system and the one previously explored is that the C(8)-position already bears an equatorial oxygen substituent, so remote functionalization would thus provide the oxidation state found in the natural product. In the event, alcohol **2.313** was treated with iodobenzene diacetate and molecular iodine and irradiated with a tungsten filament light bulb (150 W) to give protected lactol **2.316** in 94% yield. Deprotection of lactol **2.315** was effected by TBAF buffered with AcOH to give the free lactol **2.316** in 95% yield. CsF in DMF was also effective at completing the desilylation, however, the

reaction time was much longer and epimerization of the C(5)-ester stereocenter was significant. The issues of epimerization of the C(5)-stereocenter would obviously not have been an issue if the decarboxylation was performed on the initial cycloadduct, however, we recognized that the decarboxylation of **2.315** is also possible.

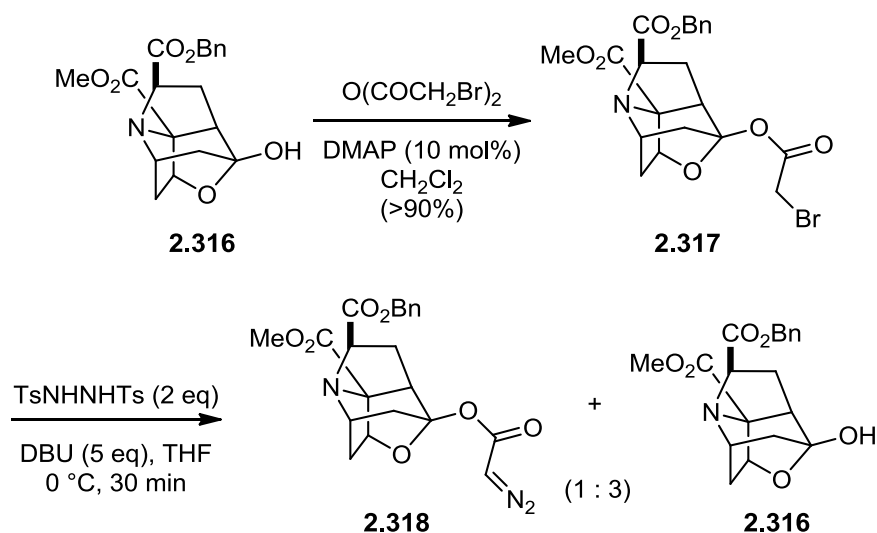
Scheme 2.79



We then turned our attention to functionalizing the acetal oxygen of **2.316** to install a diazoacetate which could be used to test the CH-insertion step (Scheme 2.80). We were aware of the difficulty that Overman had in functionalizing a similar acetal, where a silylation of this alcohol required TMS-imidazole at 130 °C for 24 h to access the TMS-protected hydroxyl group. We were therefore cognizant of the potential challenge in acylating this oxygen with a suitable precursor of a diazoacetate. We tried a number of different techniques including the use of *p*-toluenesulfonylhydrazone of glyoxylic acid chloride (House reagent for direct installation of diazoacetates),¹³⁰⁻¹³² chloroacetyl bromide/base, bromoacetyl bromide/base, and bromoacetyl bromide/HBr. However, in all cases, no reaction occurred. In fact, during reactions with bromoacetyl bromide, the starting material was consumed by TLC, but upon hydrolytic

workup the starting material was usually recovered. On the assumption that the basic nitrogen was reacting with the acetyl bromide faster than the acetal oxygen and thus hindering the reaction, we tried an esterification under acidic conditions with HBr in the hope that protonating the nitrogen would allow for an acid catalyzed esterification of the acetal. Indeed, we did observe small amounts of product; however, the conversion was never synthetically useful. In the end, the Steglich esterification (bromoacetic acid, DCC/DMAP) was the first procedure to provide a high yield of the bromoacetate product **2.317**.¹³³⁻¹³⁵ While we could observe the bromoacetate product by TLC, we found it to be unstable to chromatographic purification. The large amount of dicyclohexylurea byproduct was making interpretation of the NMR spectra difficult, and thus we sought a cleaner method for preparing **2.317**. The Steglich procedure is essentially the same as using an anhydride and DMAP catalyst, however, the anhydride of bromoacetic acid is not commercially available we prepared the anhydride of bromoacetic acid.

Scheme 2.80

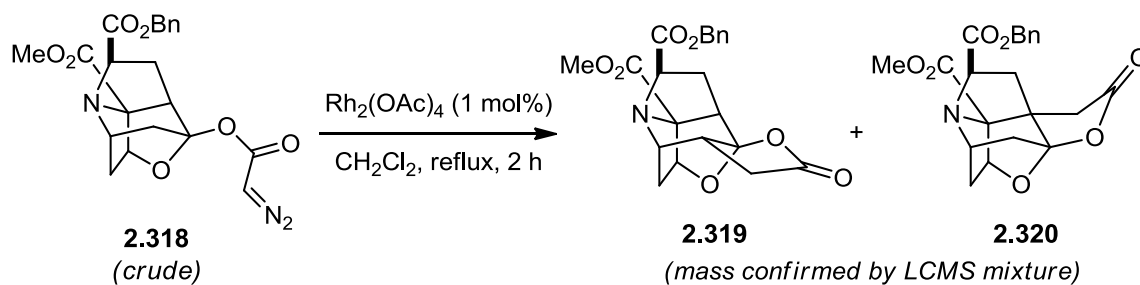


When hemiacetal **2.316** was tested with bromoacetic anhydride in the presence of a catalytic amount of DMAP, bromoacetate **2.317** was obtained in >90% yield (Scheme 2.80). Another possible approach to this reaction would be to form a mixed anhydride with bromoacetic acid and either pivaloyl chloride or i-butylchloroformate, then perform the acylation with DMAP as a catalyst. This approach would avoid the need to prepare the high boiling, hygroscopic bromoacetic anhydride since the mixed anhydride can be prepared *in situ*. Purification of **2.317** by chromatography on silica was again not possible, but the product isolated after an acid/base extraction was sufficiently pure to provide a clean ^1H NMR spectrum and was therefore used directly in the next step. Utilizing a procedure developed by Fukuyama for the preparation of diazoacetates, we next reacted bromoacetate **2.317** with bistosyl hydrazine and DBU at 0 °C for 30 min provided the crude diazoacetate **2.318**.¹³⁶ The structural assignment of diazoacetate **2.318** is still tentative at this point due to difficulties in isolating this compound in pure form. The original procedure published by Fukuyama calls for the reaction to be quenched with dilute bicarbonate; however, we found that aqueous workup in our case gave a large amount of hydrolysis to the deacylated lactol product **2.316**. Analysis of the crude reaction mixture by TLC does not show any of the lactol after completion of the initial reaction (compared to an analytical standard); however, after workup the lactol **2.316** is clearly the major constituent of the reaction mixture. It is also unfortunate that the diazoacetate **2.318** is unstable during chromatography on silica gel, which makes accessing pure diazoacetate very difficult. Attempts are currently underway to modify the Fukuyama procedure to exclude an aqueous workup; however, it will probably be necessary to carry a certain amount of impurities forward to the CH-insertion step.

Two initial attempts to perform the CH-insertion on the crude diazoacetate **2.318** have been made (Scheme 2.81). In each case the major component of the mixture that

was subjected to the insertion reaction was the lactol byproduct **2.316** from the previous step. Since the conditions of the CH-insertion call for the reaction to be performed at high dilution (0.05 M), we reasoned that this compound would not likely inhibit the intramolecular CH-insertion reaction and thus we wanted to test the reaction using materials we had in hand. Our first experiments were performed with the racemic catalyst $\text{Rh}_2(\text{OAc})_4$ to simply test the reactivity of the presumed diazoacetate. If the lactone products could be confirmed, we would have definitive proof that what we were assigning to be **2.318** was in fact the case. In the event, crude **2.318** was treated with the dirhodium catalyst, and the compound we were tentatively presuming to be the diazoacetate was consumed by both TLC and NMR spectroscopy. The ^1H NMR spectrum of the crude reaction mixture was hard to interpret with respect to the presence of the lactone product(s) **2.319** and/or **2.320** because the major component of the mixture was still the lactol impurity **2.316**. Analysis of the crude reaction mixture by LCMS, however, revealed the mass of 400 m/z which would correspond to the product of CH-insertion.

Scheme 2.81



While it is hard to be excited about these results due to their preliminary nature, the fact that the compound we were assuming to be diazoacetate **2.318** was consumed upon treatment with rhodium acetate seems to suggest that we had in fact prepared a

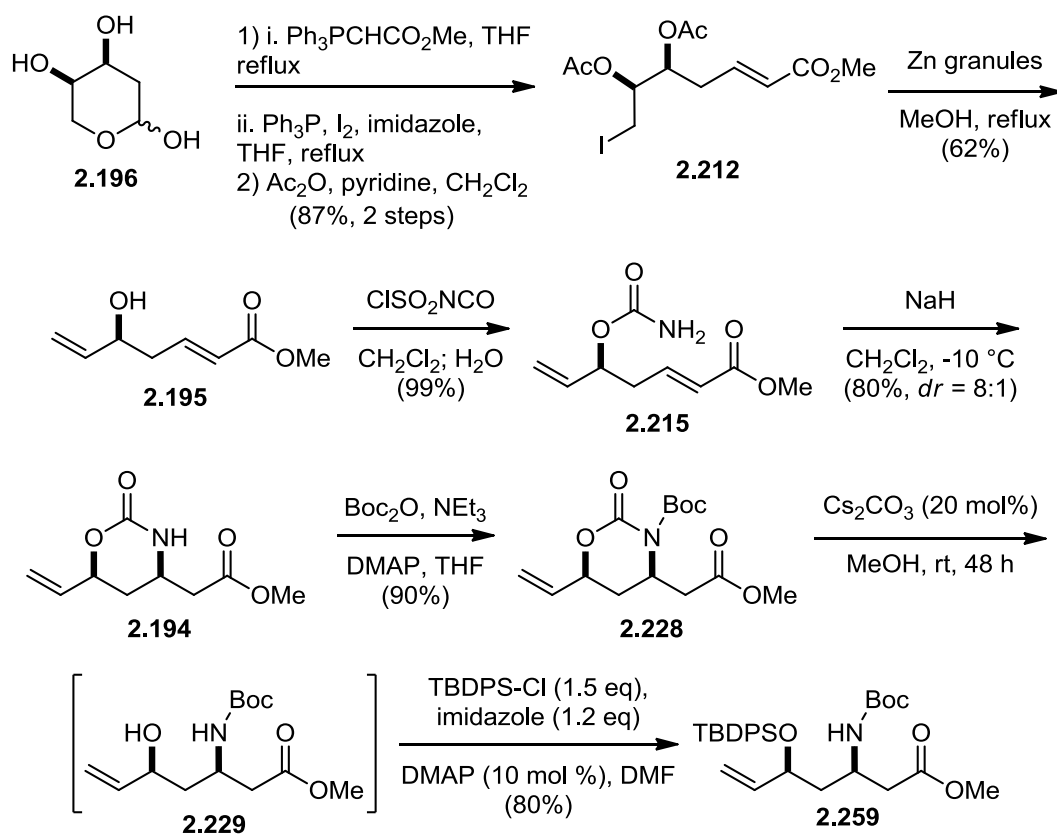
diazo compound related to our substrate. Even if the CH-insertion reaction did work to give butyrolactone, it cannot be said at this point which of the regioisomers was the major product. Based on precedent by the Doyle group, the CH-insertion reaction into the tertiary hydrogen should be inherently favored. In his work (refer to Scheme 2.77), control reactions with $\text{Rh}_2(\text{OAc})_4$ typically gave a mixture (~3:2) of lactone products favoring the tertiary insertion pathway. Further experiments will ultimately require the use of both enantiomers of the chiral Rh-MEPY catalyst in order to assess the prospect of a selective reaction.

Efforts are currently underway to access the diazoacetate **2.318** in pure form so the regioselective CH-insertion can be tested with the chiral catalysts. It is also important to note, that the system we are currently investigating is simply a model since we would first have to decarboxylate the core and install the C(3)-butenyl side chain to access the real system we are ultimately targeting.

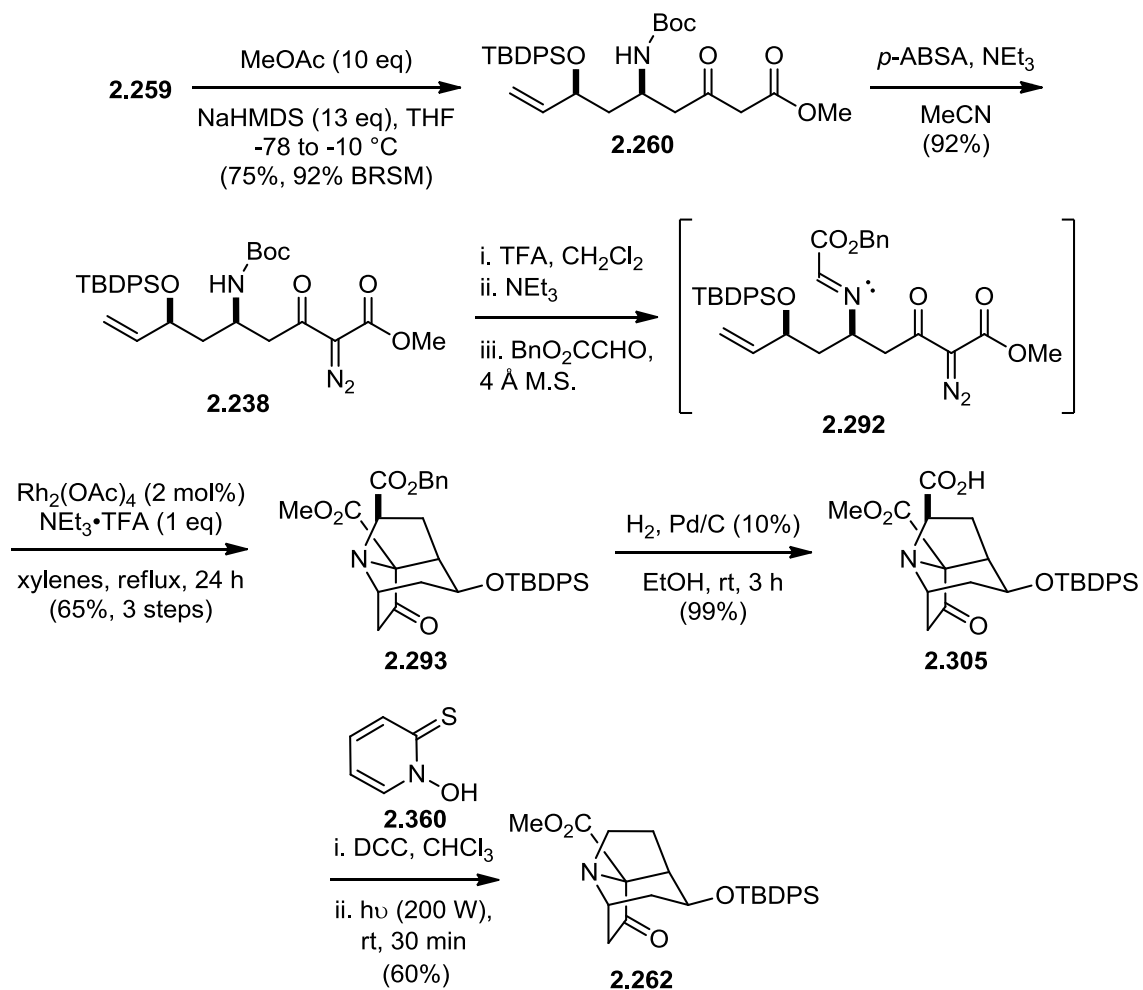
2.3 SUMMARY OF THE TOTAL SYNTHESIS TO DATE

The following section is meant to be simply a schematic summary of the Martin group total synthesis of the stemofoline alkaloids as it currently stands. The following set of reactions and conditions have been reproduced and optimized for implementation on preparative scale, and the corresponding synthetic intermediates have been fully characterized by ^1H and ^{13}C NMR spectroscopy, IR spectroscopy and high resolution mass spectrometry (HRMS). This summary concludes with the decarboxylated core structure **2.273**, and while the decarboxylation reaction has not yet been fully reproduced and optimized, this compound represents the most advanced intermediate with the most likelihood of being part of an eventual total synthesis of the stemofoline alkaloids.

Scheme 2.82. Martin Group Approach to the Stemofoline Alkaloids



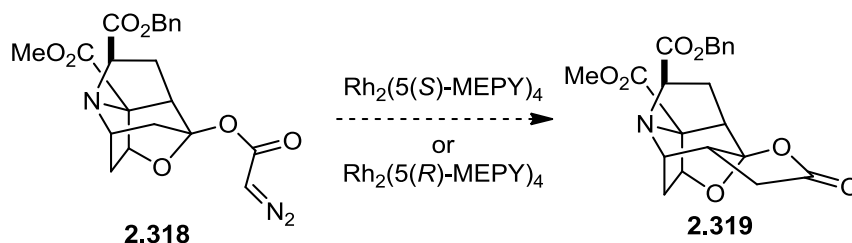
Scheme 2.83. Martin Group Approach to the Stemofoline Alkaloids Continued



2.4 CONCLUSIONS & FUTURE DIRECTIONS

A majority of my efforts toward a total synthesis of the stemofoline alkaloids were applied to designing and implementing an innovative asymmetric synthesis of the fully functionalized and oxygenated core of these alkaloids. Having accomplished that, this work has set the stage for a number of synthetic strategies going forward. Unfortunately, I have only had a little time working on the chemistry of the stemofoline core itself; however, in designing the foundation of the synthesis a number of key elements were held in mind with respect to the group's eventual endgame. By designing in the C(8)-alcohol a number of different credible synthetic plans are now at our disposal to finish the total synthesis. One approach that has recently become high on our list of priorities is the utilization of a chiral dirhodium catalyzed regioselective CH-insertion reaction to install the pivotal lactone ring. My efforts to this point have taken us up to a model diazoacetate **2.318**, which is currently being used to scout conditions for this key step (Scheme 2.81), which could potentially be applied to a more advanced intermediate in future work. This is where my efforts on the stemofoline project stand.

Scheme 2.84



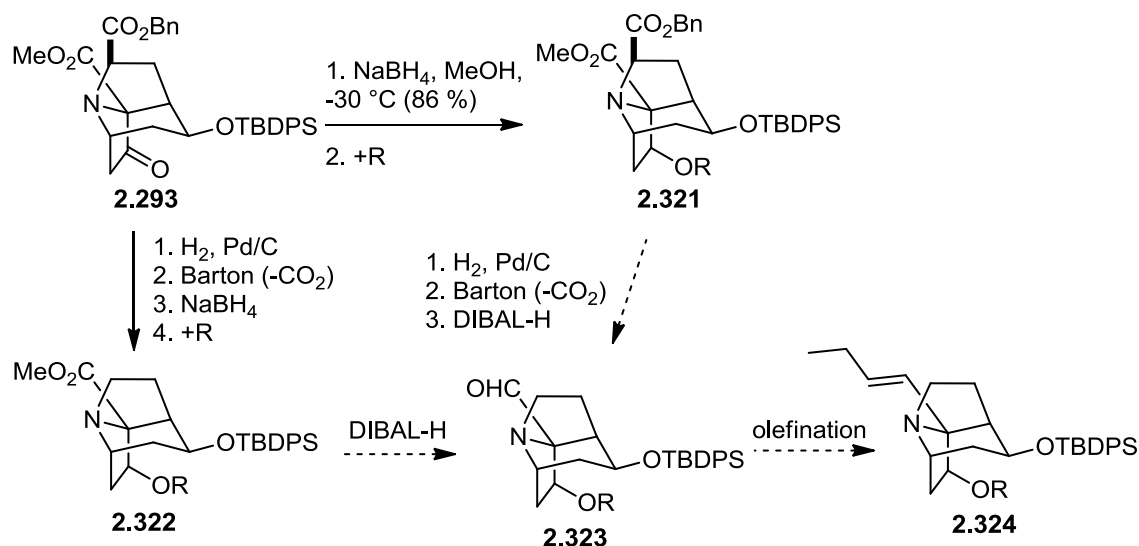
The following are my thoughts as to how one might approach finishing the total synthesis using the synthesis as it stands today. This proposal focuses on the utilization of a common intermediate to test a number of potential strategies with the emphasis of

ultimately being the development of novel chemistry. In order to complete the synthesis one will need to use the route outlined in Section 2.3 to synthesize a large quantity of the core structure **2.293**. After the initial scale up effort, compound **2.324** would be prepared as the logical next target in that it is envisioned to be a highly versatile intermediate (Scheme 2.85).

With quantities of **2.293** in hand, a number of different pathways to access the targeted lactone **2.73** can be envisioned including, but not limited to, the CH-insertion centered approach. Two obvious pathways to compound **2.324** are possible starting from cycloadduct **2.293**. The first pathway to access **2.324** has been partially scouted in that the stereoselective reduction of the pyrrolidinone ketone in the presence of the epimerizable ester has been solved. A protection of the alcohol would then necessitate the application of a Barton decarboxylation approach on the doubly protected diol of the carboxylic acid of **2.293**. This process may be more well behaved than when ketone was applied to the radical decarboxylation, but other than a slight increase in overall yield this route does not necessarily present an advantage to accessing **2.324**. The route to **2.322** would require an immediate Barton decarboxylation before the ketone is reduced and protected, which has already been successfully accomplished. Some additional work will be required, however, to increase the yield of the Barton reaction on this intermediate. Both routes would inevitably access compound **2.323**, but the order of steps is flexible. Ester **2.322** would then be reduced to give the aldehyde **2.323**. An exhaustive reduction/oxidation approach can be used, but here DIBAL-H is proposed to access the aldehyde directly. Typically when partial reductions of esters with DIBAL-H works best to give the corresponding aldehyde an α - or β -heteroatom is present in the molecule, presumably helping to increase the longevity of the tetrahedral intermediate following the reduction. Compound **2.322** has an α -nitrogen so it stands to reason that this compound,

and similar intermediates, would be ideally suited to a direct reduction. With aldehyde **2.323** in hand, a Julia-Kocienski olefination would deliver the key intermediate **2.324**.

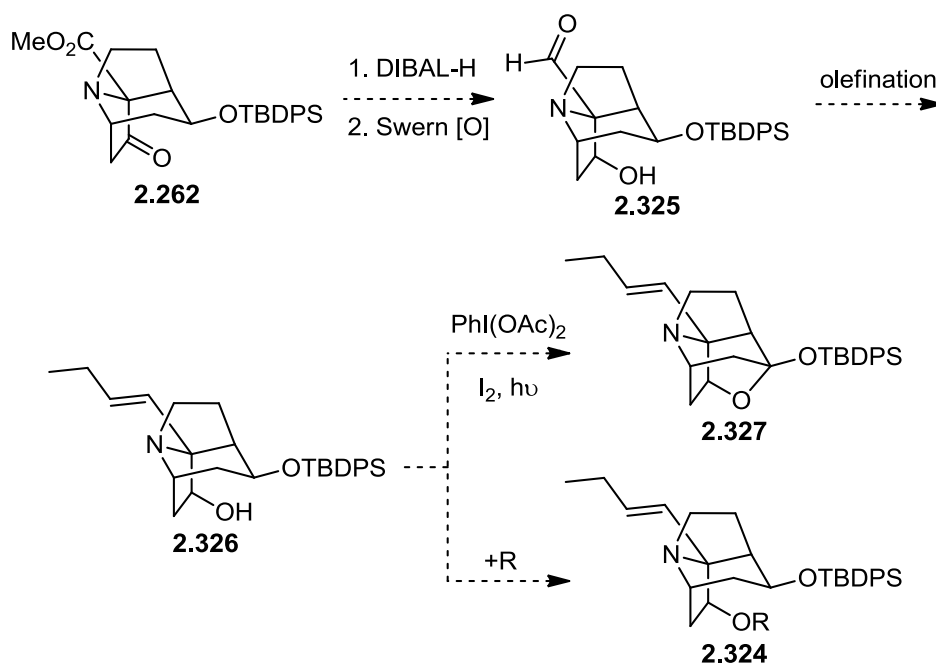
Scheme 2.85



Another approach to prepare **2.324** is slightly more aggressive and has the potential to cut two steps from the synthesis, but hinges on the eventual optimization of the Barton decarboxylation reaction on the cycloadduct **2.293** without having to reduce and protect the ketone moiety (Scheme 2.86). An exhaustive reduction of the decarboxylated cycloadduct **2.262** with either DIBAL-H or LiBH_4 would deliver a diol, which could be selectively oxidized at the primary alcohol to furnish aldehyde **2.325**. The Julia-Kocienski olefination of **2.325** would likely require the reaction to be performed on the alkoxide of **2.325** due to the basic nature of the reaction; however, it is possible that the sulfonamide anion of the olefination reagent would react selectively with the aldehyde before any interaction with the hindered alcohol. If the alkoxide did form to some extent, it is likely that the acid/base equilibrium would still favor enough of

the sulfonamide anion to facilitate the overall transformation. The olefination reaction of **2.325** would thus deliver alcohol **2.326**, which could be exploited to prepare either the key intermediate **2.324** or protected lactol **2.327**. The preparation of lactol **2.327** in this way would be the most efficient conceivable way to access this compound, which would be useful depending on the success of the CH-insertion strategy.

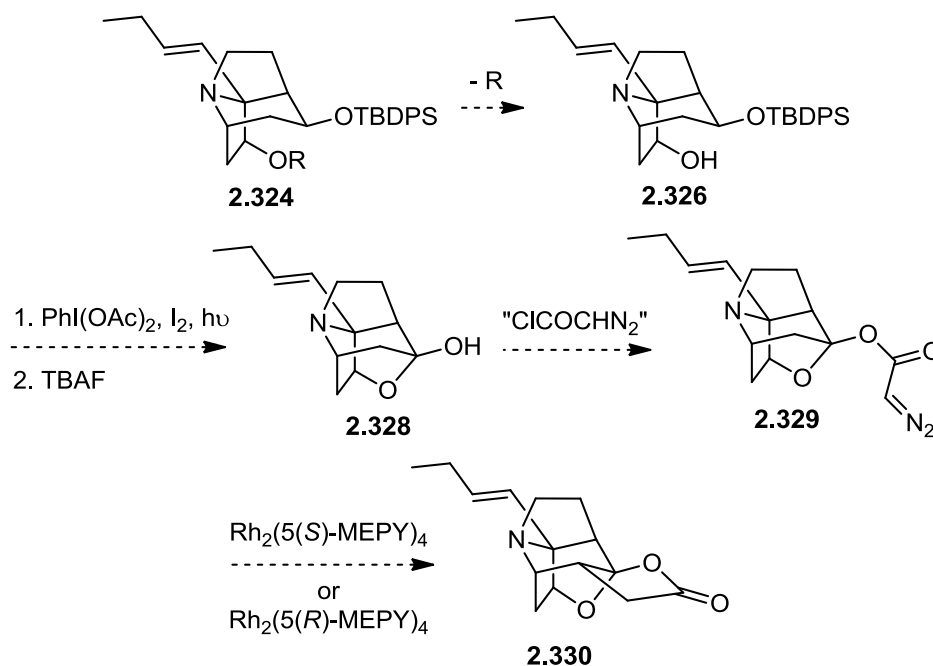
Scheme 2.86



Once intermediate **2.234** is available, a number of different vectors can be investigated simultaneously to achieve the ultimate goal of preparing lactone **2.73**. The first approach, and arguably the most novel, would be the CH-insertion approach. There are two conceivable ways to apply this key disconnect, the first being the preparation of a diazoacetate of hemiacetal **2.329** (Scheme 2.87). Deprotection of the lower alcohol would provide alcohol **2.326**, which could then be elaborated into lactol **2.328** by first applying the precedented Suarez remote functionalization of the C(8)-position followed

by disilylation. There are a variety of ways to install the target diazoacetate moiety; however, preliminary studies suggest the Fukuyama approach might be viable to access **2.329**. Implementation of the appropriate chiral dirhodium catalyst would provide lactone **2.330** via a regioselective CH-insertion into the C(9)-secondary equatorial CH-bond.

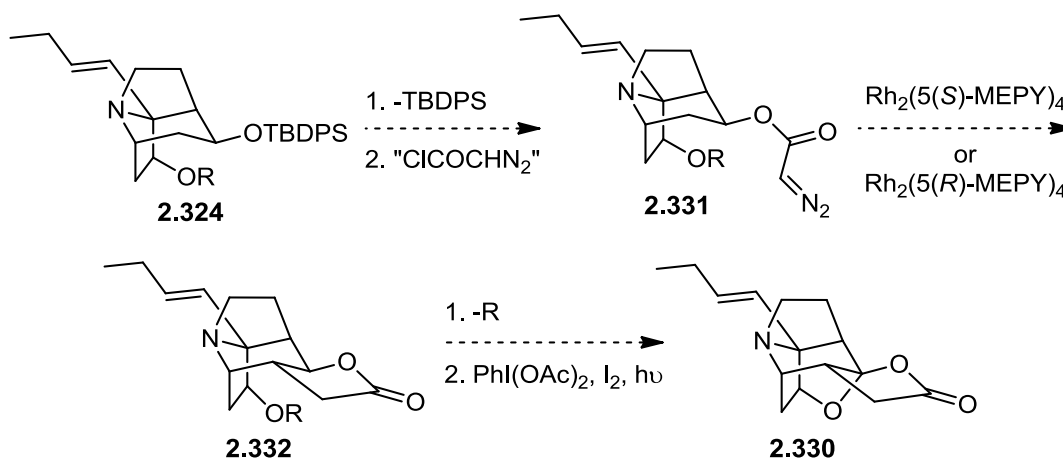
Scheme 2.87



Another possibility for accessing lactone **2.330** would be to perform the CH-insertion much earlier in the sequence on an alcohol derived diazoacetate **2.331** (Scheme 2.88). This approach does not provide an obvious advantage from the perspective of step count; however, diazoacetates of alcohols are very well known and would likely be easier to prepare and consequently more stable than the diazoacetate of the aforementioned lactol. Increased stability would most likely allow for a simplified purification procedure since diazoacetates of alcohols are known to be stable to aqueous workup and

chromatography. Also positioning the CH-insertion reaction earlier in the synthesis would inevitably make solving this problem easier due to an increased availability of material for study. This strategy would begin with the deprotection of **2.324** to give a secondary alcohol, which could be subjected to a variety of synthetic methods to provide diazoacetate **2.331**, including direct installation using the Corey modification of the House protocol.¹³⁰⁻¹³² Next, the regioselective CH-insertion reaction could be studied on the potentially better behaved **2.331** to furnish lactone **2.332**. Deprotection of the alcohol would then allow a Suarez remote functionalization to provide **2.330** bearing the appropriately oxidized C(8)-center. Moving the remote functionalization step to after the CH-insertion would not only make the CH-insertion reaction easier to test, but remote functionalization reactions into carbons bearing acetylated alcohols are very well preceded in the literature and should work comparably to the other examples of this reaction on similar substrates.

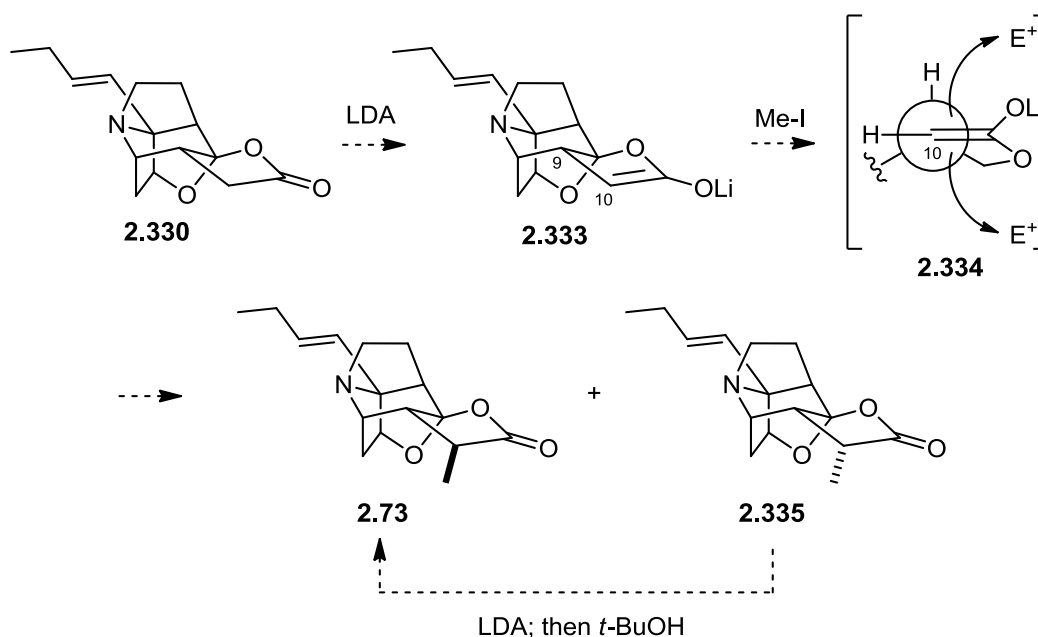
Scheme 2.88



With the pentacyclic core of stemofoline **2.330** in hand, the next major concern would be the stereoselective installation of the C(10)-methyl stereocenter (Scheme 2.89).

While the alkylation of the lactone **2.330** should be fairly easy to perform, it is unclear what, if any, stereochemical preference will predominate. Thus two possible diastereomers **2.73** and **2.335** should be expected. In analyzing the Newman projection of the C(9)/C(10)-bond there are two possible steric interactions that can be identified to make an argument for either of the two products. Attack from the bottom face appears to be the more hindered approach when considering a full 3D-model of enolate **2.334**, however, 1,2-steric influences tend to preponderate other steric affects in most reactions. Assuming the approach of the electrophile is approximately 80-90° with respect to the enolate, then a clear interaction with the C(9)-hydrogen can be seen which may have the effect of ultimately favoring alkylation from the undesired bottom face. Accurately predicting the outcome of this reaction cannot be done with any certainty; but, if any selectivity can be achieved one way or the other, a stereochemical inversion could be used to recycle the undesired product **2.335** to afford **2.73**.

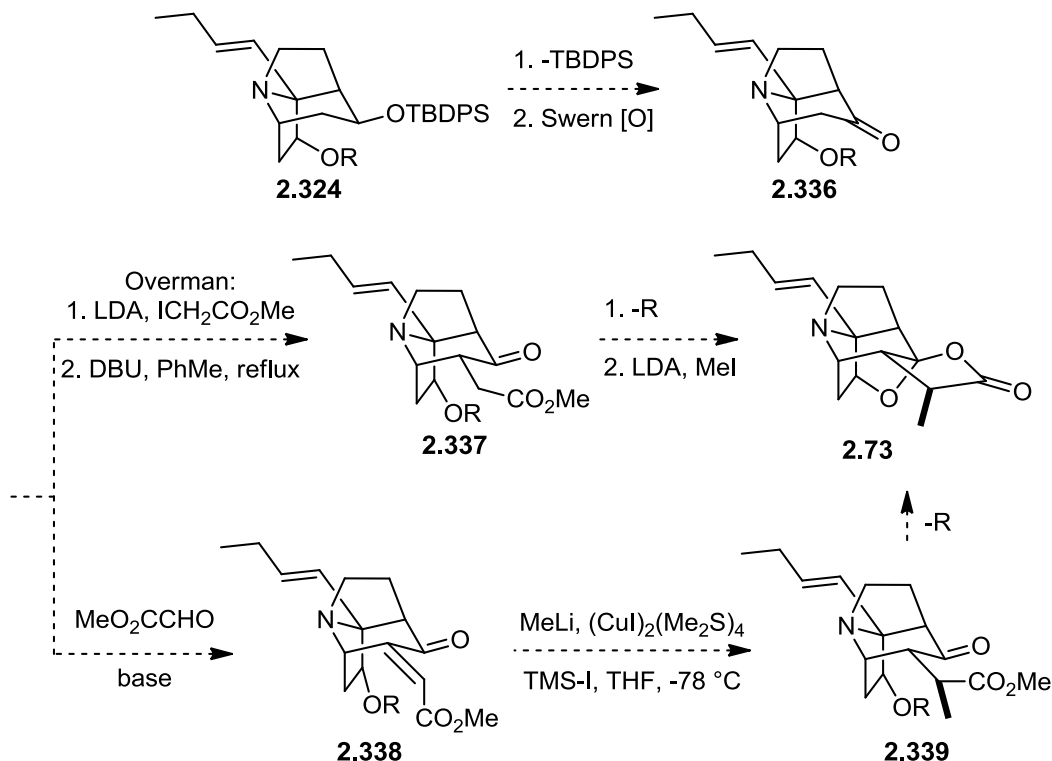
Scheme 2.89



One of the main reasons the intermediate **2.324** should be initially targeted in any future synthetic efforts is that this intermediate can also be used to explore complimentary avenues to install the C(9)-sidechain as well as the full pentacyclic core without the use of the CH-insertion reaction (Scheme 2.90). The following can be thought of as back up plans should the CH-insertion reaction not work as proposed. Also these additional routes are considerably more precedented for the stemofoline core, which might prove useful for simply advancing material to lactone **2.73** to study the ambitious final butenolide installation step while the details of the more challenging CH-insertion approach are investigated. Compound **2.324** can quickly be advanced to ketone **2.336**, by desilylation and oxidation of the secondary alcohol. It should also be noted that the analogue of **2.336** where R=Me would constitute a formal total synthesis of didehydrostemofoline (**2.3**) by intercepting an Overman intermediate in asymmetric fashion. Ketone **2.336** can also be manipulated borrowing from the Overman enolate alkylation strategy for installation of the C(9)-sidechain by first alkylating the enolate of **2.336** with methyl iodoacetate, then performing a stereochemical inversion with DBU to provide **2.337**. Unmasking the alcohol by removal of the R-protecting group would facilitate an acetalization/lactonization cascade to give lactone **2.330**, which could then be utilized in the abovementioned alkylation reaction to afford lactone **2.73** (refer to Scheme 2.89). This approach, based on the precedent established by Overman, is a virtually guaranteed way to access quantities of **2.73**, which again could be useful in studying the key final step while the details of the preceding CH-insertion strategy were worked out. Ketone **2.335** could also be utilized in a strategy that borrows from the Kende endgame, however, in this case it seems likely that a Knoevenagel condensation with methyl glyoxylate would give **2.338**. Kende utilized this same reaction to install the C(9)-sidechain with furfural to give an enone which was utilized in a highly

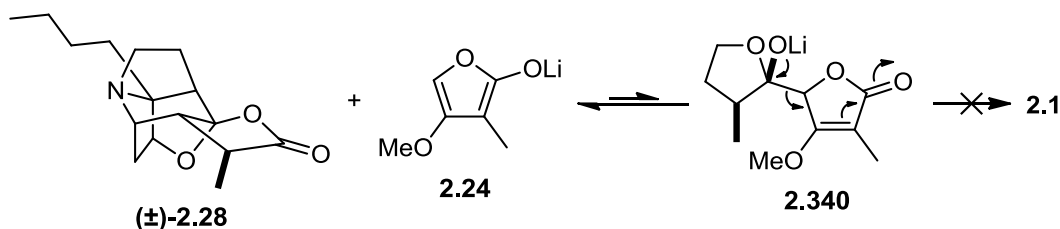
stereoselective conjugate addition to construct the C(10)-methyl stereocenter. It is therefore conceivable that enone **2.338** could similarly be subjected to a conjugate addition utilizing Bergdahl conditions to effect a regioselective 1,4-addition into the doubly activated olefin. We have previously applied these conditions to a similar conjugate addition where the olefin bore an imide and ester carbonyl and we showed that the conjugate addition was selective for the position beta to the more electrophilic carbonyl group (refer to Scheme 2.31). In this case a regioselective conjugate addition into the position beta to the more electrophilic ketone also appears to be the less sterically encumbered mode of attack making **2.339** the most likely product from this reaction. Removal of the R-protecting group from **2.339** would facilitate an acetalization/lactonization cascade to give **2.73**.

Scheme 2.90



Once an approach to **2.73** is devised, the final construction of the butenolide moiety can be implemented. The approach of installing the butenolide by addition of a furanone into lactone **2.73**, however, does not come with a complete reassurance. Kende had inadvertently prepared a similar lactone racemic **2.28**, and purportedly investigated the direct addition of the lithium furanone **2.24** as a way to access the butenolide moiety (Scheme 2.91). The problem with this type of approach, however, is that the furanone only reversibly adds to the lactone to give the tetrahedral intermediate **2.340**. The reverse reaction of expulsion of the aromatic furanone anion is considerably more favored and thus obviated the use of this approach to the synthesis of racemic stemofoline (**2.1**).

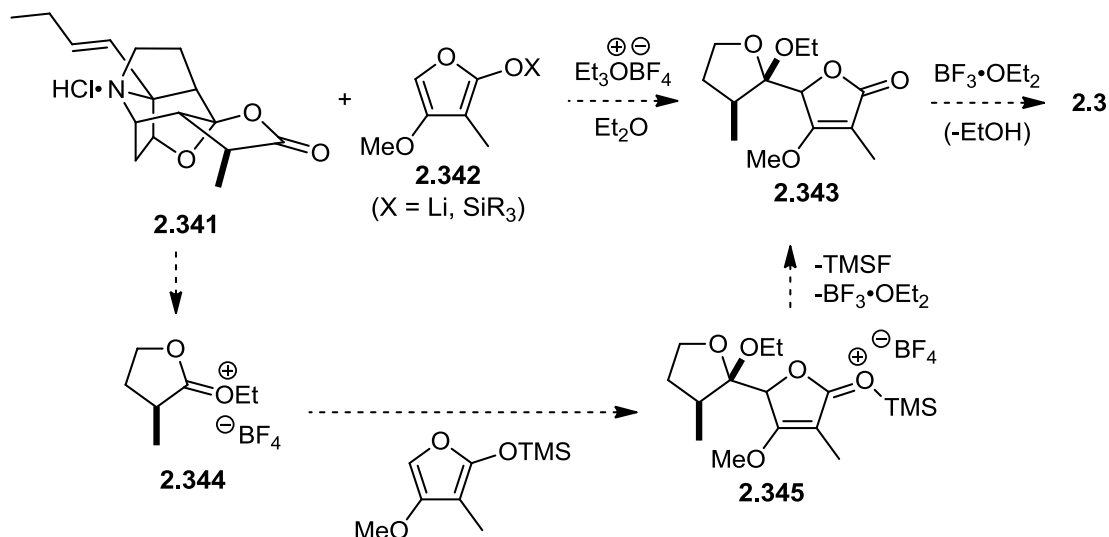
Scheme 2.91



A long standing goal in the Martin group sought to address the inherent problem of utilizing lactone **2.73** as a direct intermediate in a total synthesis (Scheme 2.92). While Kende's work ruled out a direct furanone addition, we were aiming to preactivate the lactone in such a way as to directly access a capped tetrahedral intermediate such as **2.343**. One such tactic would be the treatment of lactone **2.73**, most likely as its ammonium salt, with Meirwein's reagent, which would hopefully alkylate the lactone to provide an intermediate oxonium ion such as **2.344**.¹³⁷ This intermediate would then be reacted with either the lithium furanone or siloxyfuran of **2.342** to give **2.343** directly, which bears a capped oxygen atom, thus removing the possibility of the troublesome retro-addition reaction. If the siloxyfuran of **2.342** is used then addition into the oxonium

ion **2.344** would deliver a silylated oxonium ion such as **2.345**. It is then conceivable that the tetrafluoroborate counterion anion could serve to desilylate the silyl oxonium ion thus liberating TMS-F and $\text{BF}_3 \cdot \text{OEt}_2$. Tetrafluoroborate salts are known in the literature to desilylate labile silyl groups, and thus it would seem the silyl oxonium ion **2.345** would fall well within the reactivity of tetrafluoroborate. This desilylation would produce an equimolar amount of a strong Lewis, which might therefore serve to eliminate a molecule of ethanol thus delivering the butenolide moiety of didehydrostemofoline (**2.3**).

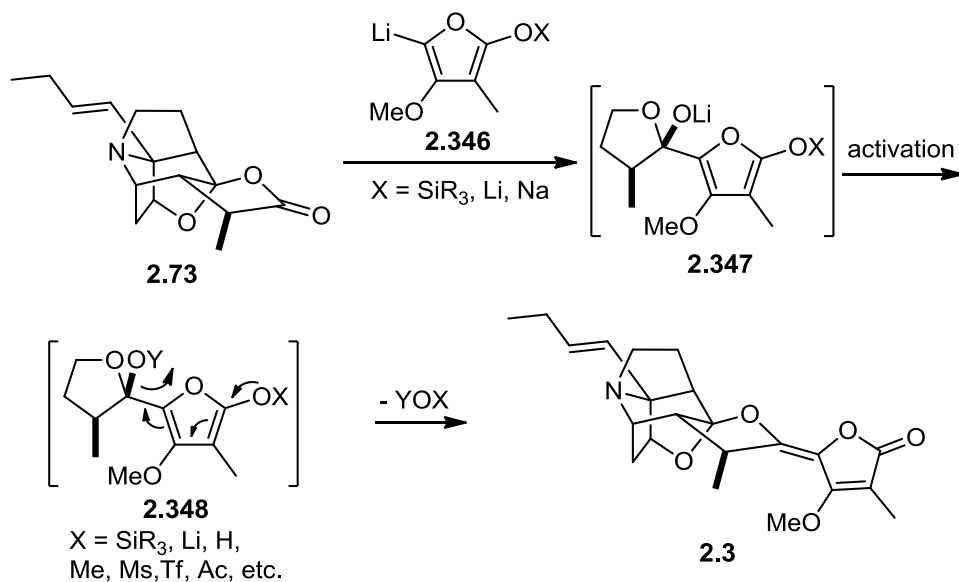
Scheme 2.92



A final, more direct approach to installing the butenolide moiety would bypass the problem of adding the furanone into the lactone thus delivering a potentially unstable intermediate such as **2.340** or **2.345**. Since the furanone anion itself is such a good leaving group due to its aromatic nature, it is likely that any attempt to add the furanone into the lactone directly will be met only with limited success. To remove this problem altogether, the metallofuran ion **2.346** could be used as a nucleophile thus providing the considerably more stable furan addition product **2.347**, which would not allow for the

retro-addition process to occur because the leaving group would have to be an sp^2 anion (Scheme 2.93). This addition reaction could conceivably be performed with the siloxy metallofuran of **2.346** or the dianion (either Li or Na/Li) of **2.346**. Activation of the alkoxide intermediate **2.347** would then facilitate the expulsion of the newly generated leaving group. Considering that this leaving group is alpha to an oxygen atom and a very electron rich aromatic group, it should be very facile towards elimination and thus deliver didehydrostemofoline (**2.3**) in one single operation. With the dianion ($X = \text{Li}$ or Na), it is also possible that no activation will be required since elimination of lithium and sodium oxides is known to occur in certain circumstances. In the proposed system the elimination reaction is highly geared to occurring, since the transition state involved in expulsion of the leaving group can be stabilized by four different electronically conjugated oxygen atoms.

Scheme 2.93



The preceding discussion regarding the end game of the Martin group total synthesis of stemofoline was meant to serve as a guide for the next researcher who takes on this very challenging project. Due to a great deal of effort that went into developing an efficient, cost-effective, and scalable synthesis of the stemofoline core, the future of this project is indeed brighter than it has such a strong foundation from which to build upon. It should also be noted that the reactivity established in the key dipole cascade cycloaddition reaction is unique among total syntheses involving the use of a 1,3-dipolar cycloaddition reaction of an azomethine ylide (see Chapter 1 for full discussion of this topic). Not only did we successfully apply a 1,3-dipolar cycloaddition to access a very sterically demanding caged substrate, but the key cycloaddition was accomplished through a very efficient cascade reaction that assembled three rings and three stereocenters in a single operation from an acyclic starting material. Upon completion of the total synthesis of these alkaloids, the Martin group synthesis will take its place among the premier examples of the application of 1,3-dipolar cycloaddition chemistry in the field of natural product total synthesis.

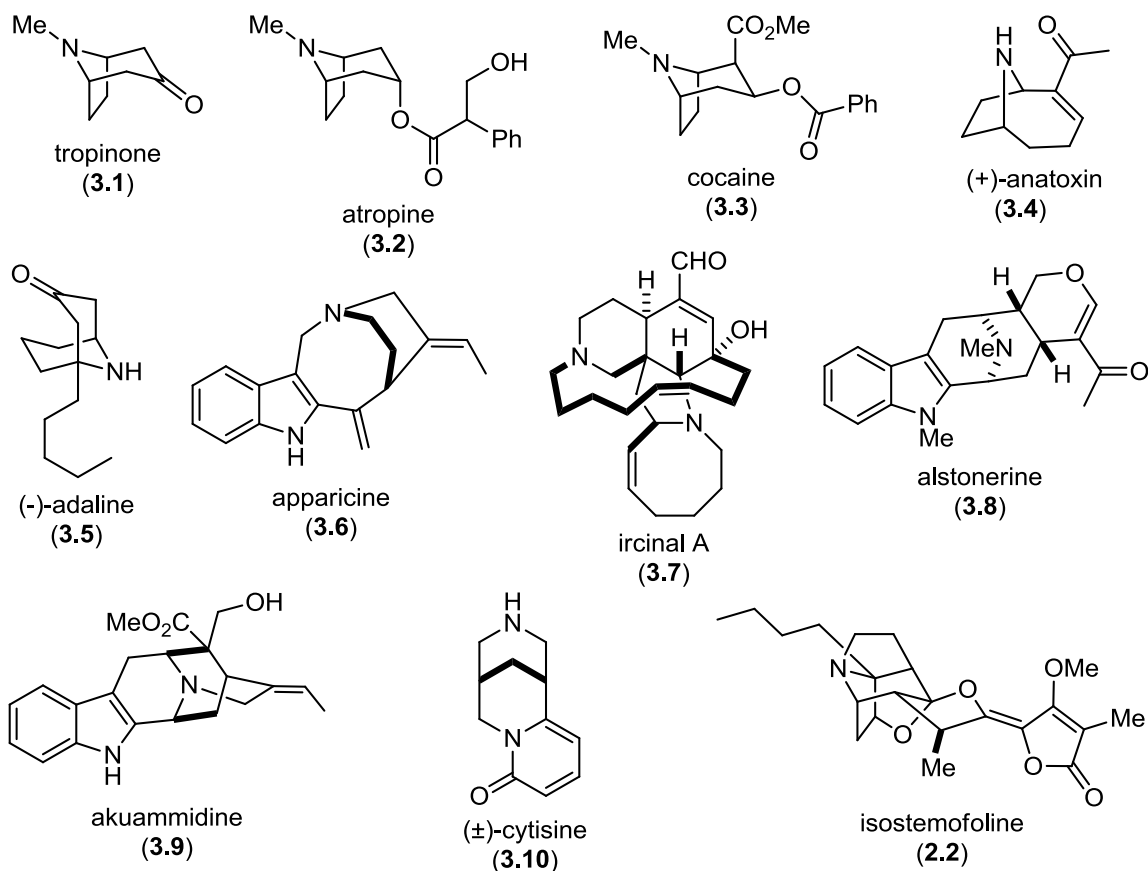
Chapter 3 – The Application of the Pauson-Khand Reaction as a Novel Entry into the Synthesis of Bridged Azabicyclic Scaffolds

3.1 INTRODUCTION

3.1.1 Naturally Occurring & Biologically Relevant Bridged Azabicyclic Molecules

The first synthesis of tropinone (**3.1**) by Willstätter in 1903 spurred over a century of continuous study on the chemistry of bridged azabicyclic (BAzB) molecules;¹³⁸⁻¹⁴⁰ and, to this day, continues to be the target of investigation by research groups interested in the synthesis of nitrogen containing natural products. The ubiquity of these types of ring systems in biologically active natural product skeletons makes it easy to understand why the synthesis of BAzB ring systems remains at the forefront of synthetic chemistry (Figure 3.1).

Figure 3.1 - Selected Bridged Azabicyclic Natural Products

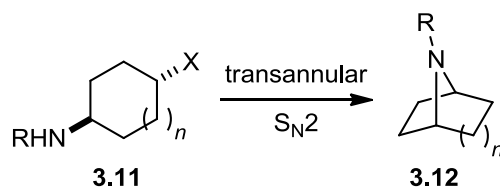


3.1.2 Synthetic Approaches to Bridged Azabicyclic Ring Systems via Transition Metal Mediated Processes

3.1.2.1 Classic Approaches

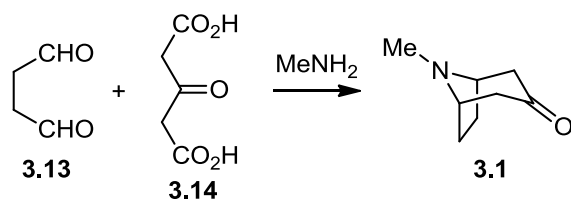
While leaving a lot to be desired, the Willstätter synthesis of tropinone established the efficacy a transannular S_N2 reaction to construct the BAZB motif. To this day, the use of transannular substitution reactions of amines such as **3.11** remains one of the most common techniques to synthesize this class of molecules (**3.12**, Scheme 3.1).

Scheme 3.1



In 1917, Robinson published his own approach to tropinone which accomplished the synthesis in one step from succinaldehyde (**3.13**), acetonedicarboxylic acid (**3.14**), and methyl amine (Scheme 3.2).¹⁴¹ The Robinson tropinone synthesis, considered a veritable classic in organic synthesis, utilized the Mannich reaction as the key disconnect in constructing the tropinone core. The Mannich reaction, being arguably one of the most widely used transformations in natural product synthesis, also continues to be of critical importance to the synthesis of BAzB systems.

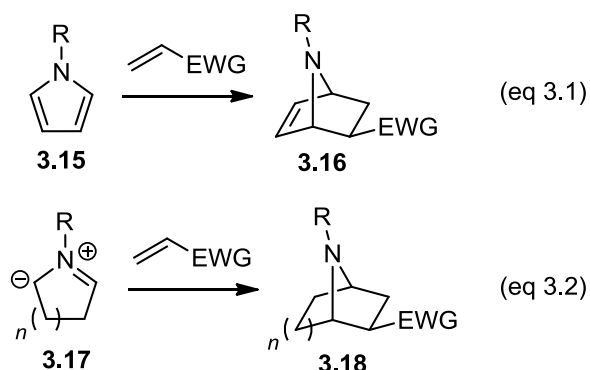
Scheme 3.2



Another classic way to construct BAzB structures is by the application of both inter- and intramolecular cycloaddition reactions of nitrogen containing compounds (Scheme 3.3). The [4+2]-cycloadditions of pyrroles such as **3.15** and dipolarophiles for example, is a very useful technique for constructing bridged azobicyclo-[2.2.1]-scaffolds (Scheme 3.3, eq. 1). Another type of cycloaddition, which is incredibly versatile, is the 1,3-dipolar cycloaddition reactions of azomethine ylides such as **3.17**. This transformation can ultimately be used to access a larger variety of bicyclic frameworks in

that the starting heterocycles used to form the ylide is not limited to 5-membered rings (Scheme 3.3, eq. 2).

Scheme 3.3



While this summary in no way does justice to the sheer breadth of work that has been done in the area of BAZB synthesis, it does serve to outline the basic reactivity that has been relied on most heavily. The more modern approaches, discussed herein, which focus on the use of transition metal catalyzed/mediated processes, have brought a great deal to the table in this field, and provide a number of unique and versatile strategies to the synthetic organic chemist.

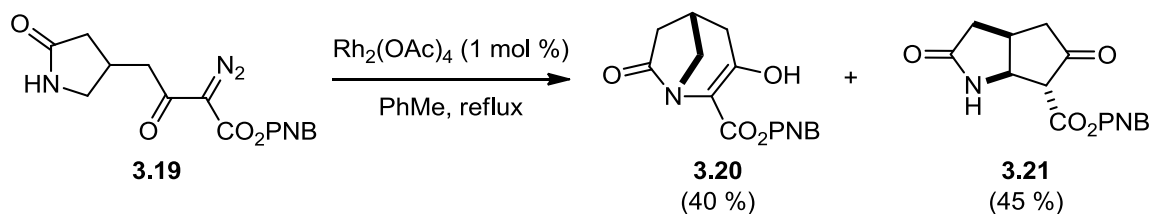
3.1.2.2 Rhodium - Intramolecular Carbene Insertion Reaction

The study of the chemistry and reactivity of diazo compounds has provided the synthetic community with a great deal of useful synthetic methodologies.¹⁴² The vast majority of these studies focused on harnessing the powerful reactivity of the carbene species resulting from metal mediated diazo decomposition reactions. A variety of transition metals can be used to induce diazo decomposition to form metal carbenoid intermediates, including rhodium, copper, palladium, and ruthenium, among others. The

most commonly studied catalysts for these types of transformation, however, tend to be dirhodium complexes. While the use of dirhodium catalysis to form bridged carbocyclic and bridged oxobicyclic ring systems by CH-insertion reactions is well known, the use of CH-insertion reactions in the formation of BAZB has not been meaningfully studied. It is possible, however, to form BAZB ring systems by the process of intramolecular NH-insertion reactions.

A report by Aventis Pharmaceuticals illustrated that lactams tethered to diazo- β -ketoesters such as **3.19**, when treated with catalytic rhodium acetate, delivered the so-called “anti-Bredt” lactam **3.20** in 40% yield along with the product of CH-insertion to form the fused bicycle **3.21** (Scheme 3.4).¹⁴³ A number of other examples were also investigated in this study with varying substitution patterns, and all provided similar results for the BAZB ring system.

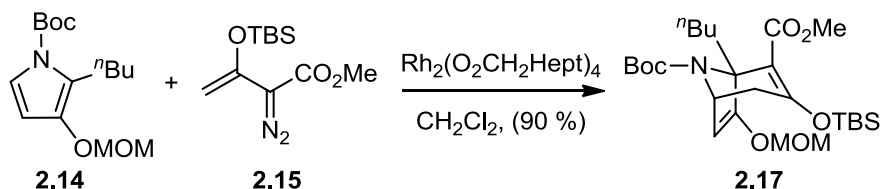
Scheme 3.4



Another example comes out of the Kende total synthesis of isostemofoline (**2.2**) in which a rhodium catalyzed formal [4+3]-cycloaddition between pyrrole **2.14** and vinyl diazoacetate **2.15** provided the bridged azabicycle **2.17** (Scheme 3.5).⁷³ The application of this reaction in the context of a isostemofoline total synthesis was discussed in the previous chapter (Chapter 2). The general methodology used by Kende was developed by the Davies group for the synthesis of bridged oxabicyclic compounds;⁷⁸ however, the

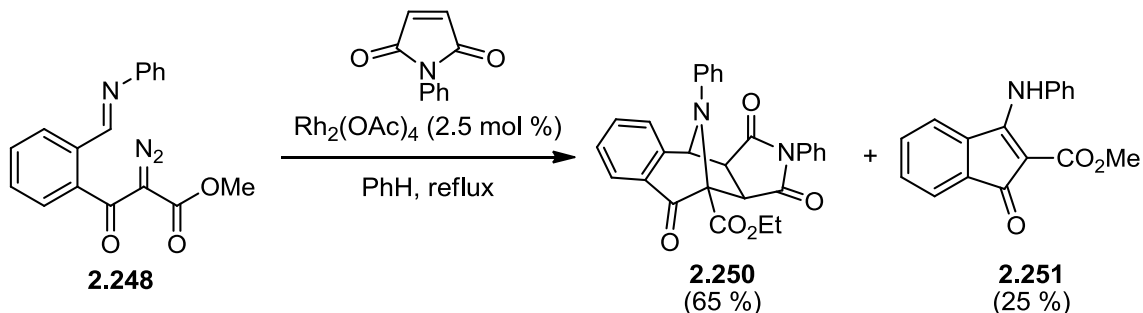
Kende variant remains the lone application of this method to a BAZB ring system. It stands to reason, that this method could easily find an application in other settings.

Scheme 3.5



The work of the Padwa group over the years have served to greatly expand the scope of diazo chemistry considerably. One intriguing example of his work was in the reaction of the imine tethered diazo-β-keto ester **2.248** that, when exposed to catalytic rhodium acetate, reacted in an intramolecular fashion to provide an azomethine ylide that underwent a 1,3-dipolar cycloaddition with N-phenylmaleimide (Scheme 3.6).¹²⁷ This reaction provided the BAZB compound **2.250** in 65% along with 25% of the CH-insertion product **2.251**. The application and expansion of this methodology was discussed in the previous chapter in the context of a Martin group total synthesis of the stemofoline alkaloids (Chapter 2).

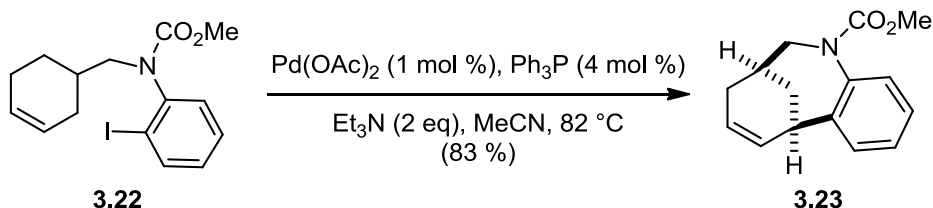
Scheme 3.6



3.1.2.3 Palladium - Intramolecular Heck Reaction

The Overman group has championed the use of the intramolecular Heck reaction as a way of synthesizing a broad range of hetero- and carbocyclic frameworks.¹⁴⁴⁻¹⁵⁰ Since the early studies on this methodology, the intramolecular Heck reaction has been applied successfully to many different natural product total syntheses. In one of his early reports in this area, the Overman group applied this budding technology to the synthesis of the BAZB molecule **3.23** (Scheme 3.7).¹⁵¹ Treatment of aryl iodide **3.22** with Pd(OAc)₂ and Ph₃P facilitate an intramolecular Heck reaction onto the appended cyclohexene moiety to provide the bridged scaffold in 83% yield. This initial reaction served to establish the efficacy of this methodology to the synthesis of BAZB ring systems, and has since been applied very broadly to tackle the synthesis of complex BAZB compounds.

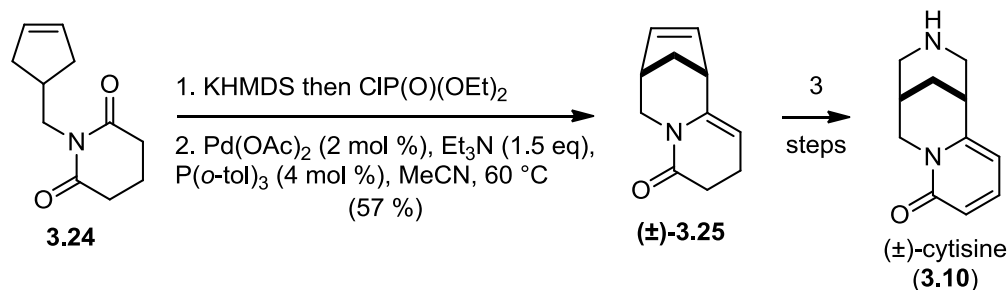
Scheme 3.7



The Pfizer laboratories reported the application of the intramolecular Heck reaction to the synthesis of the BAZB natural product cytisine (**3.10**, Scheme 3.8).¹⁵² The N-alkyl glutarimide **3.24** was first converted to the corresponding vinyl phosphonate, and the crude material was treated with catalytic Pd(OAc)₂ and P(o-tol)₃ to facilitate an intramolecular Heck to furnish the BAZB compound **3.25**. In an effort to perform this Heck reaction in an asymmetric sense, they were also able to develop a one-step protocol

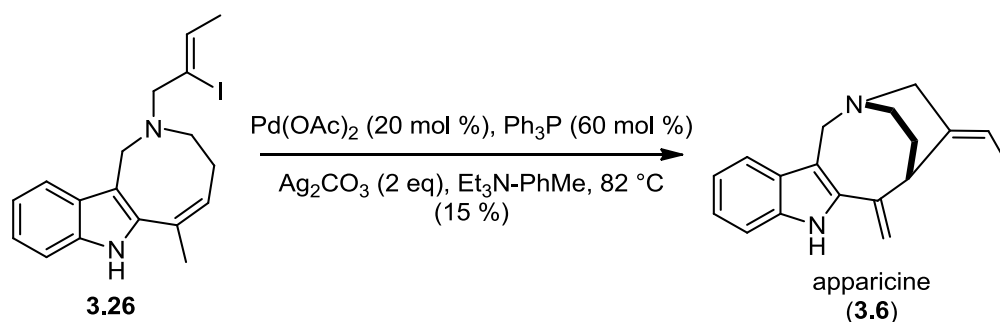
from **3.24** with a chiral phosphine ligand. While the asymmetric Heck only provided low chiral induction (22% *ee*), the one-pot protocol shorted the overall total synthesis to a total of five steps providing racemic cytosine (**3.10**) in high overall efficiency.

Scheme 3.8



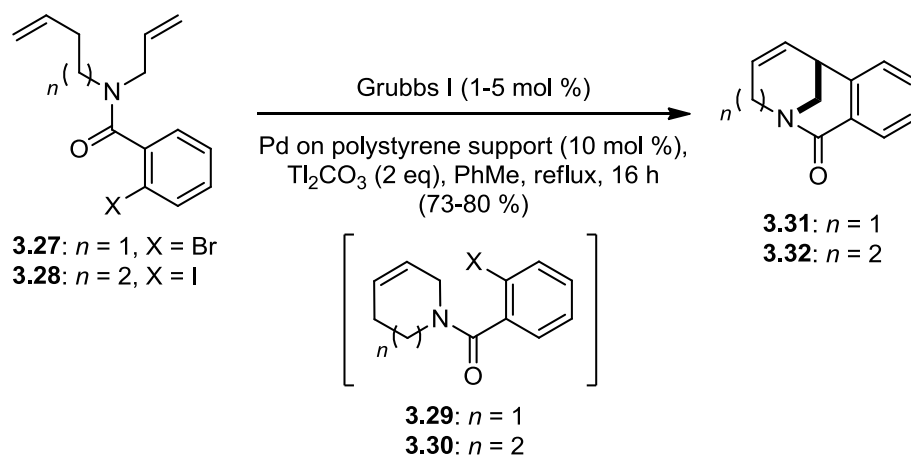
The Bennasar group total synthesis of apparicine (**3.6**, Scheme 3.9) aimed to employ a very demanding intramolecular Heck reaction to the synthesis of the strained BAZB natural product scaffold.¹⁵³ Treatment of vinyl iodide **3.26** with catalytic Pd(OAc)₂ and Ph₃P under cationic conditions managed to successfully effect a Heck reaction on the tethered olefin to construct the apparacine ring system, albeit in very low yield. They surveyed a great deal of Heck conditions to accomplish this transformation; however, only the cationic conditions with silver carbonate provided any of the desired product. This example of the intramolecular Heck reaction serves as encouragement that the Heck can be successfully used to apply very strained molecules while illustrating the limitation of this methodology.

Scheme 3.9



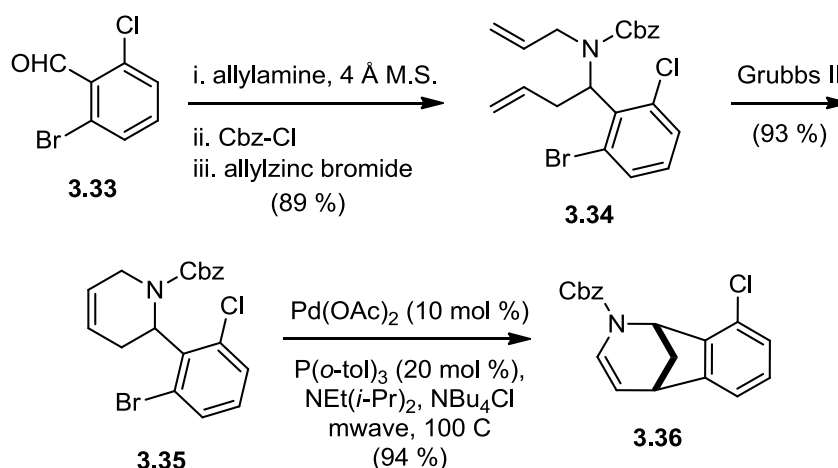
A notable synthetic method reported by Grigg, applied the intramolecular Heck reaction as part of a RCM/Heck cascade process for the construction of “anti-Bredt” lactams such as **3.31-3.32** (Scheme 3.10).^{154, 155} Treatment of dienylarylhalides of type **3.27-3.28** with Grubbs first generation catalyst provided an intermediate piperadine **3.29-3.30**, which was subjected to Heck conditions to effect formation of the BAZB scaffold. When this sequence was performed sequentially (RCM then Heck), yields of 48-55% were obtained for bicycles **3.21** and **3.22**; however, by performing this sequence as a tandem bimetallic process the same products were attained in much improved yields of 73-80%. Performing the cascade reaction with a $\text{Pd}(\text{OAc})_2$ precatalyst and Ph_3P was unsuccessful due to poisoning of the ruthenium catalyst, thus the use of polystyrene bound palladium was required to physically separate the catalysts.

Scheme 3.10



A recent example from the Martin group has illustrated the feasibility of the intramolecular Heck reaction to rapidly construct the norbenzomorphan skeleton **3.36** (Scheme 3.11).¹⁵⁶ In this approach, the Martin group multicomponent assembly strategy was utilized to quickly access diene **3.34**, which was then subjected to RCM to provide the piperadine **3.35** in 83% overall yield. Treatment of the bisarylhalide with $\text{Pd}(\text{OAc})_2$ and $\text{P}(o\text{-tol})_3$ under microwave irradiation furnished the BAZB compound **3.36** in excellent yield. This overall synthetic approach provides an excellent complement to the Grigg's strategy, and it stands to reason that the bimetallic cascade reaction he developed would be similarly effective on this scaffold.

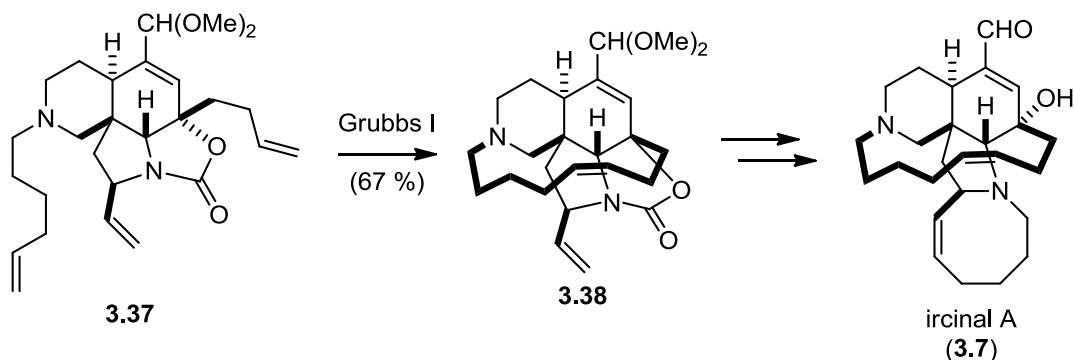
Scheme 3.11



3.1.2.4 Ruthenium - Ring Closing Metathesis

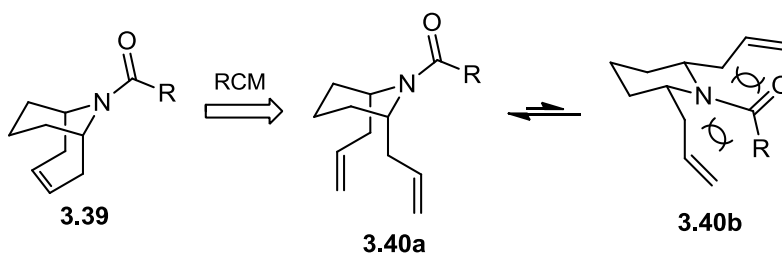
As discussed in the previous section, the RCM reaction is an effective tool for the synthesis of heterocyclic compounds. The featured RCM examples were used to set up intramolecular Heck reactions in the construction of BAZB scaffolds. Significant work in the synthetic community has focused on use of the RCM itself as a general tool to directly construct BAZB molecules. The first such feat was accomplished by the Martin group in the total synthesis of ircinal A (**3.7**) in 1999 and subsequently manzamine A in 2002 (Scheme 3.12).^{157, 158} The treatment of triene **3.37** with Grubbs first generation catalyst facilitated an RCM to form the macrocyclic BAZB molecule **3.38**, which was subsequently converted to ircinal A (**3.7**) and manzamine A. This reaction served as useful precedent going forward that the RCM could be used to access structurally demanding BAZB ring systems.

Scheme 3.12



Building upon the aforementioned RCM to access the manzamine core, the Martin group set out on a series of synthetic studies to develop a general synthetic method for the synthesis of BAzB ring systems using this reaction as the key disconnect.¹⁵⁹⁻¹⁶¹ Cognizant of the fact that N-acyl-2,6-*cis*-disubstituted piperadines prefer to adopt a diaxial conformation such as **3.40a** to avoid the significant pseudo- $A_{1,3}$ strain when in the diequatorial conformation **3.40b**, it was hypothesized that a dienyl substrate such as **3.40** would therefore undergo facile RCM reaction when exposed to Grubbs catalyst (Scheme 3.13).

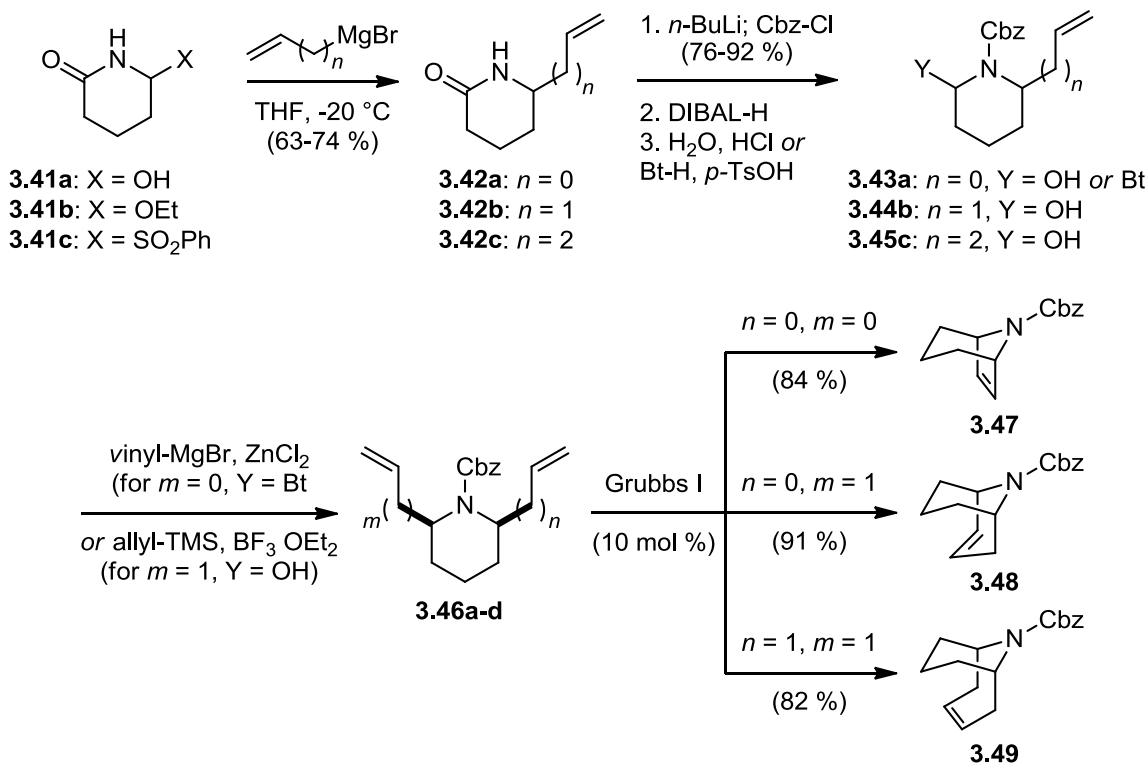
Scheme 3.13



In order to access a series of piperidine derivatives to test this concept, the gutarimide derived hemiaminals **3.41a-b** and amidosulfone **3.41c** were treated with an

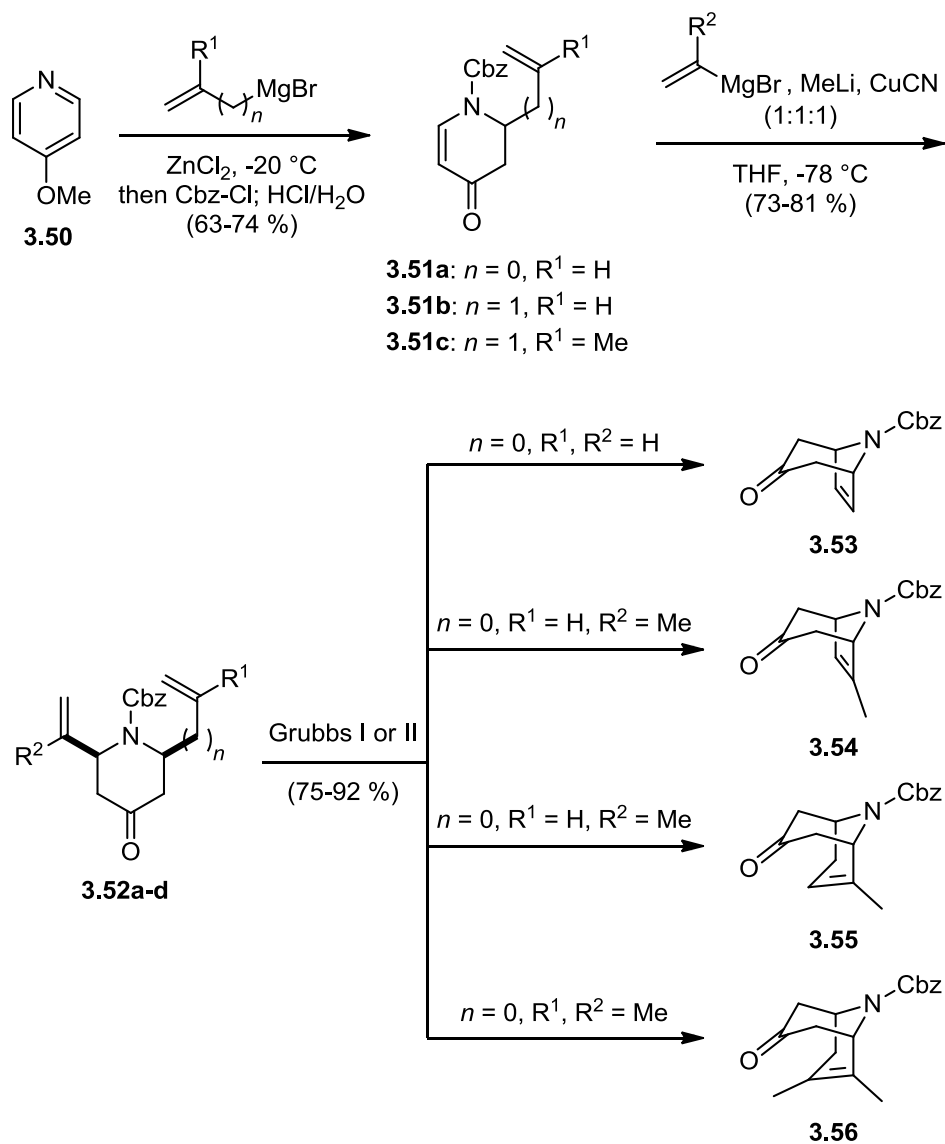
appropriate organometallic reagent to effect a Mannich reaction providing lactams **3.3.42a-c**, varying in the length of the newly installed olefin side chain (Scheme 3.14). Acylation of the lactam nitrogen, followed by reduction of the corresponding imide, provided the intermediate hemiaminals **3.43b-c**. Workup with benzotriazole (Bt-H) and tosic acid, rather than by hydrolysis, provided the more active benzotriazole leaving group **3.43a**. A second Mannich reaction with vinyl-Grignard or allyl-Grignard cleanly provided the 2,6-*cis*-disubstituted piperadines **3.46a-d**. Treatment of these dienyl piperadines with Grubbs first generation catalyst thus provided the bridged azabicyclo-[3.2.1], [3.3.1], and [4.3.1]-scaffolds **3.47-3.49** in excellent yields. All attempts to make the [5.3.1]-scaffold, however, failed to provide the BAZB system and only gave oligomeric mixtures.

Scheme 3.14



Further exploration into the scope of this reaction led the Martin group to adopt a general synthetic strategy developed by Commins for the synthesis of 2,6-*cis*-disubstituted piperadones. In applying the Commins strategy, 4-methoxypyridine (**3.50**) could be rapidly converted to a series of vinyl and allylated piperadones **3.51a-c** by addition of the corresponding organometallic reagent into the Lewis acid activated pyridine ring followed by capping the product with Cbz-Cl. A subsequent copper mediated conjugate addition provided the dienylpiperadones **3.52a-d**, whereupon treatment with Grubbs first or second generation catalysts provided the corresponding BAZB molecules **3.53-3.56** in excellent yields. This series of RCM reactions, not only illustrated the ability to incorporate additional functionality into the piperadine ring system, but demonstrated that various substitution patterns on the olefinic side chains could also be tolerated. Notably, the sterically demanding tetrasubstituted olefin **3.56** was readily synthesized by this strategy.

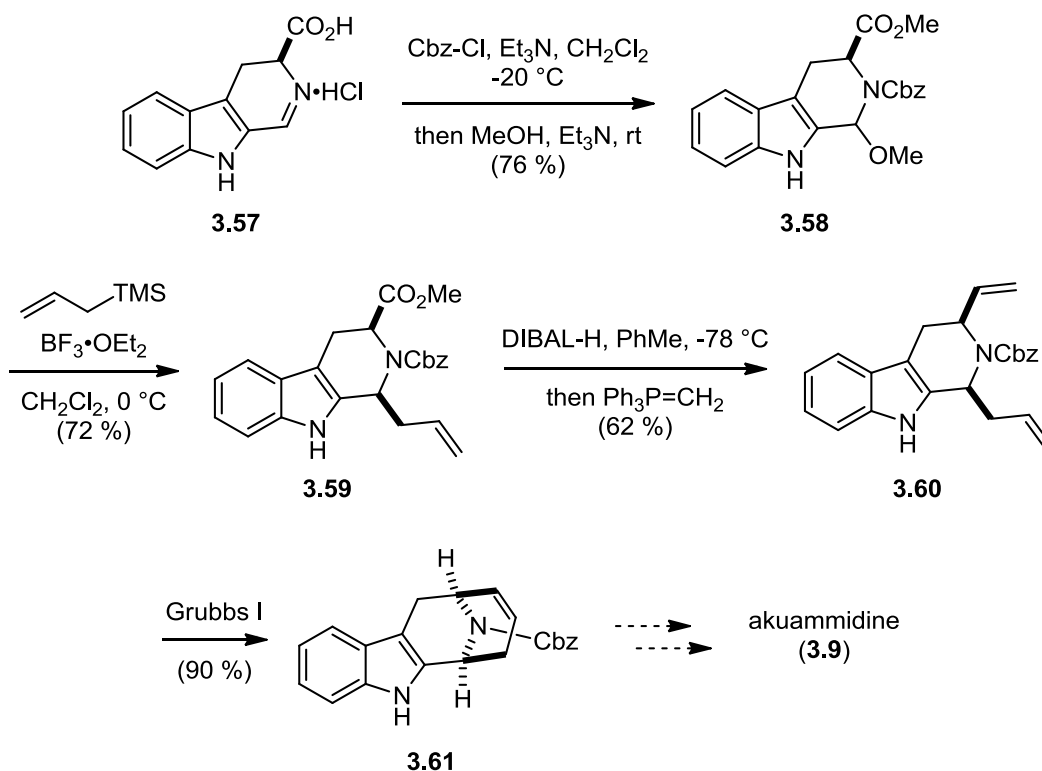
Scheme 3.15



A final extension of the Martin group RCM strategy was the synthesis of an azabridged tetrahydro- β -carboline ring system, which is an important motif in *Sarpagine* family of natural products (Scheme 3.16). Starting with β -carboline **3.57**, the imine moiety was first acylated, and resulting acyliminium ion was treated with MeOH to provide the aminal **3.58** in 76% yield as a mixture of diastereomers. Next, a Sakurai

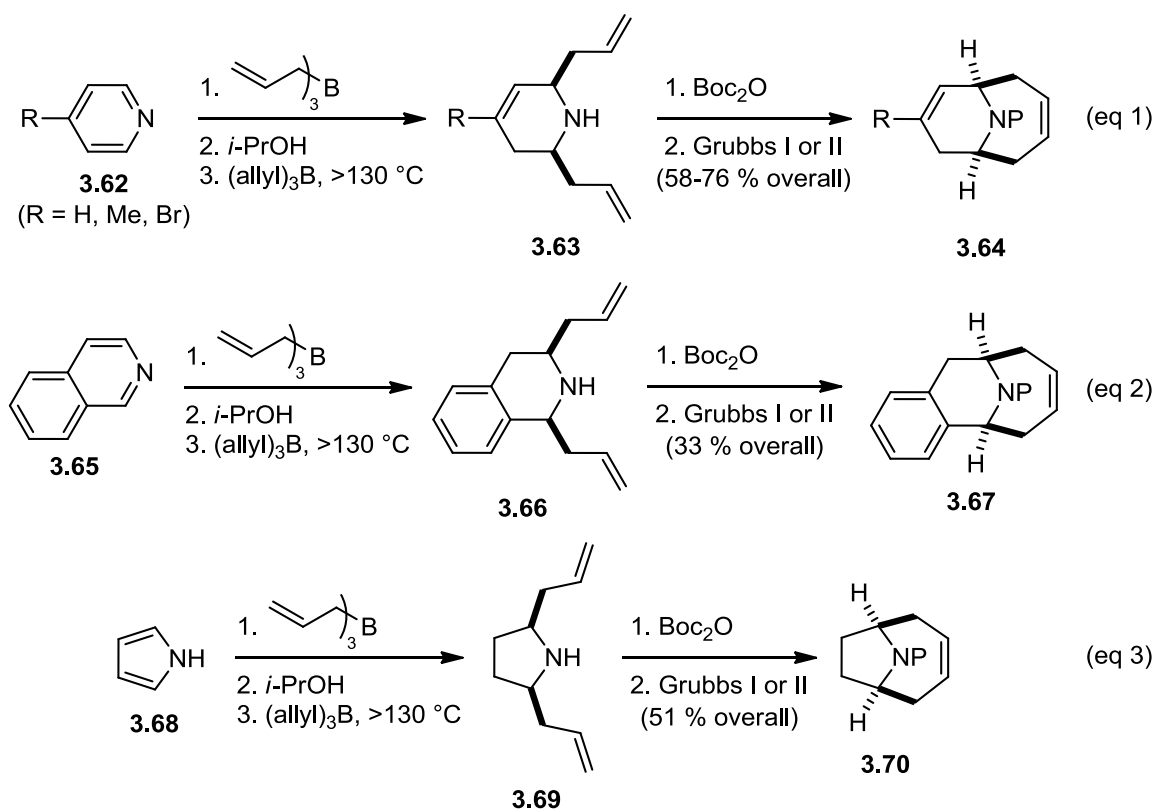
reaction furnished the allylated tetrahydro- β -carboline **3.59** in 72% yield bearing the essential 2,6-*cis*-stereochemistry. The ester was then subjected to a one-pot reduction/olefination reaction to afford diene **3.60** in 62% yield. Treatment of the diene with Grubbs first generation catalyst resulted in an RCM reaction to give the BAZB tetrahydro- β -carboline **3.61** in 90% yield. Compound **3.61** is a conceivable intermediate en route to a number of natural products including akuammidine (**3.9**). This approach to **3.61** served, not only as critical precedent for our group going forward, but as inspiration of the group's eventual total synthesis of alstonerine (discussed in Section 3.13 of this chapter).

Scheme 3.16



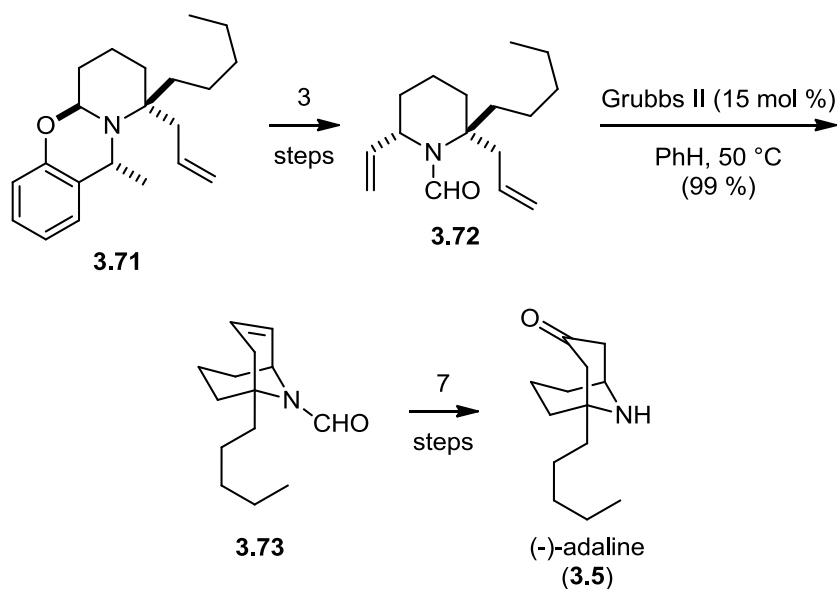
The general Martin group strategy for the synthesis of BAZB ring systems utilizing the RCM reaction has also served as inspiration for a number of other groups in their efforts to construct BAZB scaffolds. Bubnov, for example, developed a bisallylation reaction with triallylborane and heterocycles such as pyridine, isoquinoline, and pyrrole (Scheme 3.17).^{162, 163} Treatment of various 4-substituted pyridines such as **3.62** with triallylborane and *i*-PrOH provided the 2,6-*trans*-diallyl compounds, which could effectively be epimerized by an additional reaction with triallylborane under thermolytic conditions. This three step procedure ultimately provided the 2,6-*cis*-disubstituted piperadines **3.64** in short order. Boc-protection of the piperadines allowed for the required diaxial conformation to be achieved, and resulted in a high yielding RCM reaction upon treatment with Grubbs catalyst. This general strategy was also applied to access the BAZB tetrahydroisoquinoline **3.67** and the BAZB pyrrolidine **3.70**. While the Bubnov approach is very efficient, it can only provide access to the diallylated series of compounds thus limiting its general use.

Scheme 3.17



A number of natural product syntheses have been accomplished using the Martin group RCM approach to BAZB systems, including the 2002 report by the Kibayashi group on the total synthesis of (-)-adaline (**3.5**, Scheme 3.18).¹⁶⁴ The chiral aminal **3.71** was converted to the N-formyl-2,6-*cis*-diene **3.72** in three steps, which set up an RCM reaction with Grubbs second generation catalyst to furnish the BAZB compound **3.73** in virtually quantitative yield. An additional seven steps provided the natural product (-)-adaline (**3.5**).

Scheme 3.18

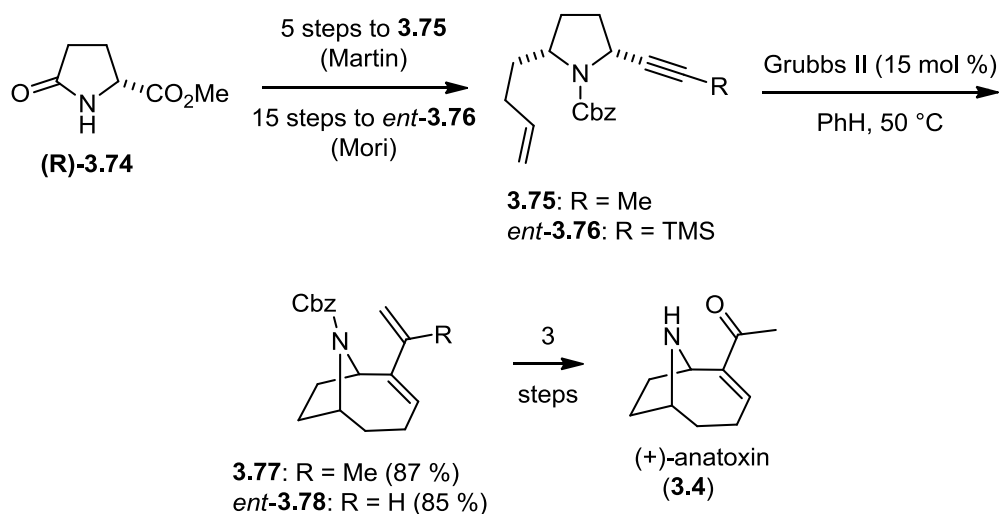


In 2004, the Martin group reported the synthesis of the BAzB natural product (+)-anatoxin-a (**3.4**) using an expansion of their RCM methodology to include an enyne RCM reaction (Scheme 3.19).¹⁶⁵ This account was joined by a paper from the Mori group on the synthesis of (-)-anatoxin-a using the same type of enyne RCM.¹⁶⁶ Aggarwal also published a remarkably similar RCM approach to (+)-ferrugine (**3.82**, Scheme 3.20);¹⁶⁷ and notably, all three of these syntheses were submitted for publication within five days of each other. Each synthesis began with a chiral pyrroglutamic acid derivative as the starting material, the stereochemistry of which was utilized to install the 2,5-*cis*-substitution in asymmetric fashion. The Martin group targeted enyne **3.75** in this way, which possessed a methyl substituted alkynyl group. Treatment of **3.75** with Grubbs second generation catalyst provided the BAzB compound **3.77** which was subsequently converted to (+)-anatoxin-a (**3.4**). Mori's approach used the TMS-capped alkyne group,

which underwent a similarly facile RCM reaction to provide the anatoxin skeleton **3.78**.

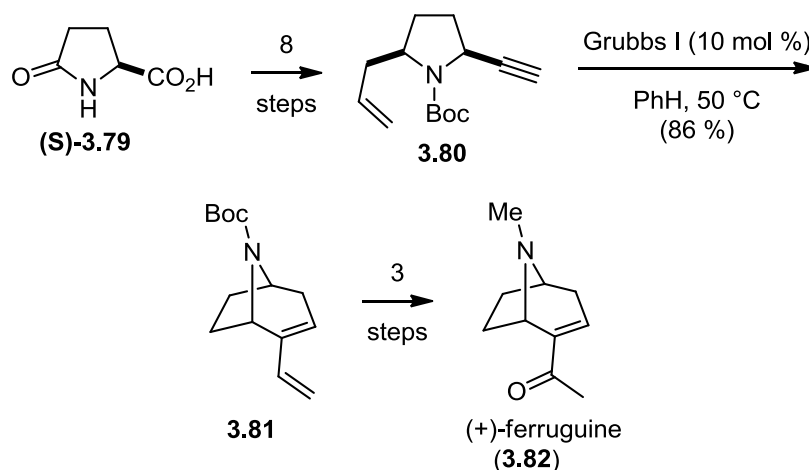
The Mori intermediate was converted to (-)-anatoxin-a.

Scheme 3.19



The Aggarwal synthesis utilized the lower homologue **3.80** to similarly access the azabicyclo-[3.2.1]-ring system of ferrugine (**3.82**, Scheme 3.20). In the event, enyne **3.80** underwent an enyne RCM with Grubbs first generation catalyst to afford **3.81** in 86% yield. Three more steps were thus required to furnish (+)-ferrugine.

Scheme 3.20



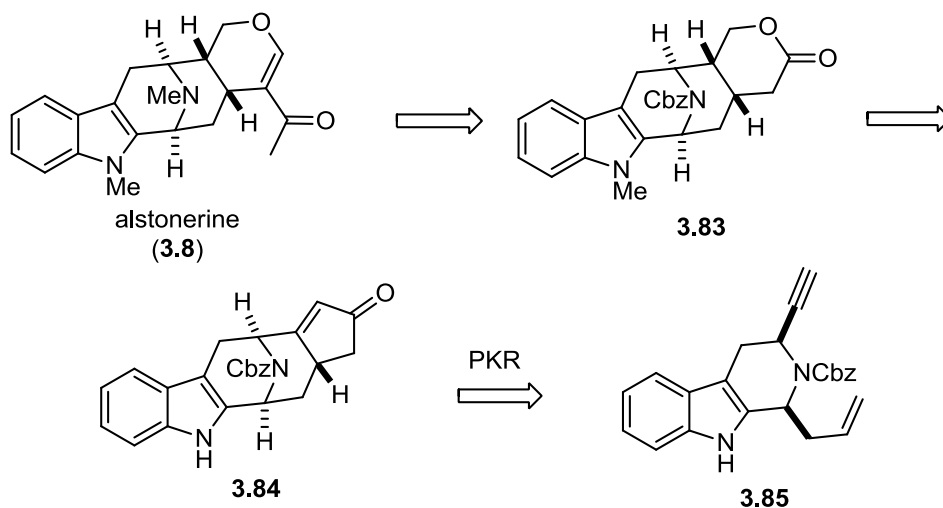
3.1.3 The Pauson-Khand Reaction as an Entry into Bridged Azabicyclic Frameworks

3.1.3.1 Introduction

Subsequent to our group's development of the RCM strategy to synthesize BAZB frameworks, we became interested in examining the possible application of the Pauson-Khand reaction (PKR) toward this goal.¹⁶⁸ The intramolecular version of the PKR has been applied to the syntheses of a few alkaloid natural products, but in each case, its use has been limited to the preparation of fused bicyclic molecules. Our synthesis of tetrahydro- β -carboline **3.61** produced a particularly interesting scaffold (Scheme 3.16), which on the surface mapped closely on to a few different *macroline/sarpagine* indole alkaloids, including alstonerine (**3.8**, Scheme 3.21). The use of an RCM to construct this scaffold we felt was a possible outlet to alstonerine, however, a successful application of a PKR reaction would provide a considerably more functionalized BAZB compound 3.333. With the ability to directly access the cyclopentenone moiety using this key

transformation we envisioned utilizing the inherent functional and carbon framework to elaborate **3.83** into the dihydropyran ring required for alstonerine.

Scheme 3.21

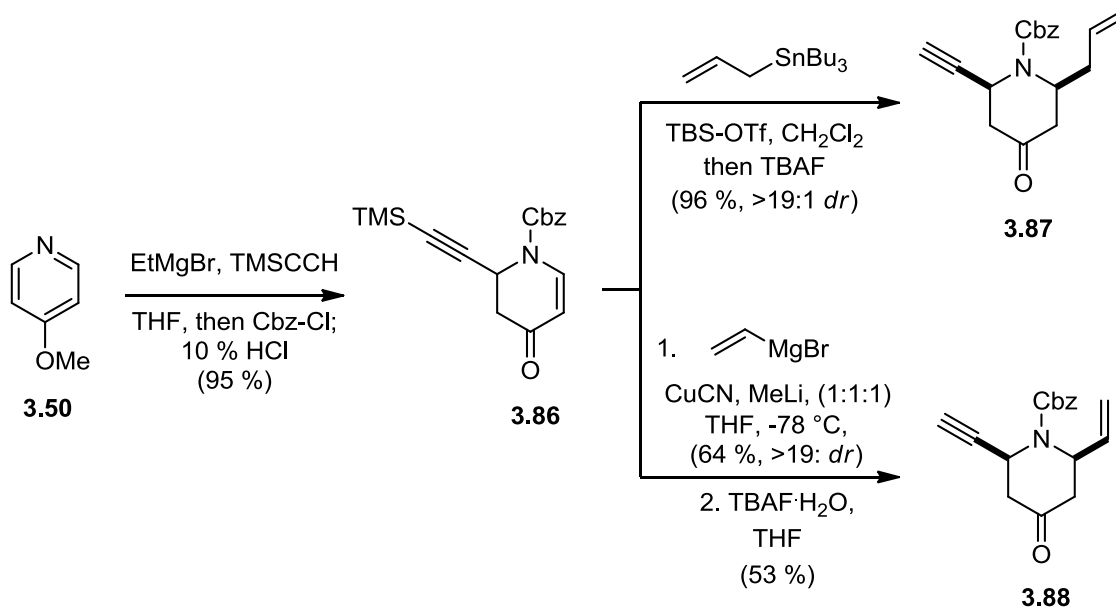


3.1.3.2 Prior Art in the Martin Group

Considering that the PKR to form bridged azabicyclic structures lacked precedent, we undertook the synthesis of a number of 2,6-*cis*-disubstituted piperidine enynes which differed in the number of carbons separating the alkene and alkyne moieties from the bridging nitrogen atom. We sought to use these enynes as substrates for Pauson-Khand reaction to assemble azabicyclo-[3.3.1] and azabicyclo-[3.2.1]-ring systems using chemistry previously utilized for the material preparation during the Martin group investigation of the comparable RCM methodology. Following the work of Comins, 4-methoxypyridine (**3.50**) was treated with the acetylide ion derived from TMS-acetylene in the presence of Cbz-Cl to provide the enone **3.86** following acidic workup (Scheme 3.22). Conjugate addition of allyl tributylstannane to **3.86** proceeded using TBS-OTf as a Lewis acid, followed by addition of TBAF to provide the enyne **3.87** in excellent yield

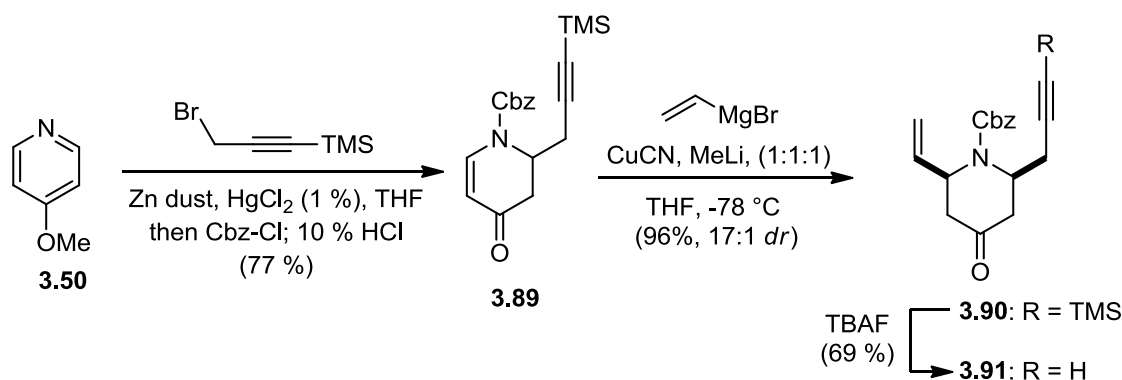
and diastereoselectivity. The enone **3.86** also underwent conjugate addition with a vinyl cuprate reagent to provide the enyne **3.68** after removal of the silyl group in high diastereoselectivity.

Scheme 3.22



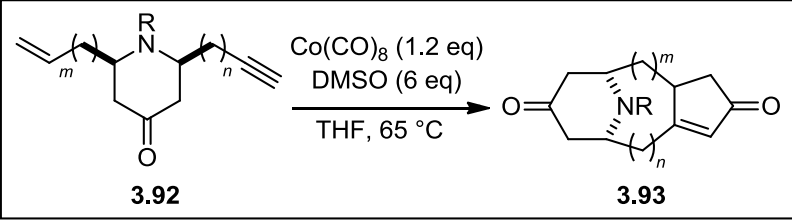
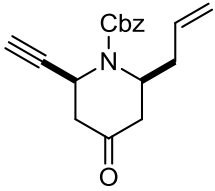
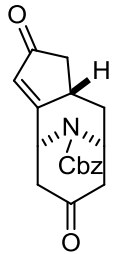
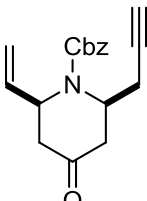
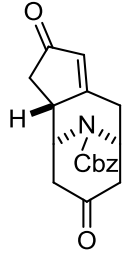
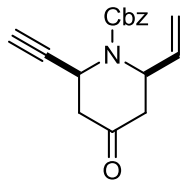
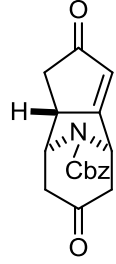
Alternatively, treatment of 4-methoxypyridine (**3.50**) with the zinc reagent derived from 1-trimethylsilyl propargyl bromide in the presence of Cbz-Cl gave the homologated enone **3.89** in good yield (Scheme 3.23). This enone underwent conjugate addition with a vinyl cuprate followed by treatment with TBAF to provide the enyne **3.91** in good yield and excellent diastereoselectivity.

Scheme 3.23



With the 2,6-*cis*-disubstituted piperidines **3.87**, **3.88**, and **3.91** in hand, the PKR of was attempted utilizing $\text{Co}_2(\text{CO})_8$ and a number of common promoters, including NMO, BuSMe, and 4 Å molecular sieves. The conditions that gave the most efficient reaction involved treatment of enynes **3.92** with $\text{Co}_2(\text{CO})_8$ to give an intermediate cobalt-complex that was then treated with six equivalents of DMSO and warmed to 65°C to give the enones **3.93** in excellent yield (Table 3.1). Optimization of this transformation revealed that use of high quality $\text{Co}_2(\text{CO})_8$ was essential to obtain high yields. Catalytic variants employing rhodium catalysts failed to provide any of the enone **14**, and typically the starting enynes **3.92** were recovered. We were comforted by the fact, however, that stoichiometric $\text{Co}_2(\text{CO})_8$ was still generally less expensive than the rhodium catalysts. With the optimized PKR conditions at our disposal, the BAZB products **3.94**, **3.95**, **3.96** were synthesized. Both **3.94** and **3.95** proceeded in high yields and provided the products as a single diastereomers, however, the more strained system **3.96** was only obtained in 33% yield and also suffered from erosion in stereoselectivity.

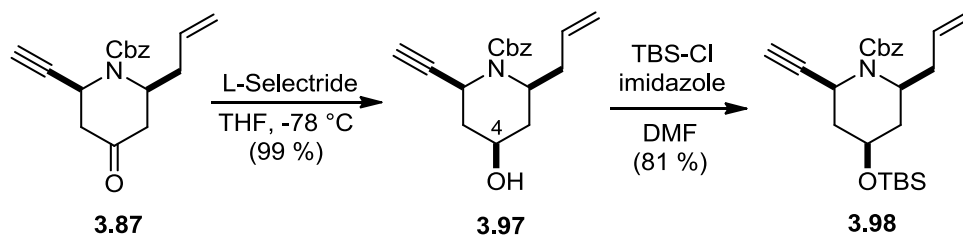
Table 3.1

<div style="border: 1px solid black; padding: 10px; text-align: center;">  <p>3.92 3.93</p> </div>			
<i>entry</i>	<i>substrate</i>	<i>product</i>	<i>yield</i>
1	 <p>3.87</p>	 <p>3.94</p>	89 %
2	 <p>3.91</p>	 <p>3.95</p>	91 %
3	 <p>3.88</p>	 <p>3.96</p>	33% (3:1 <i>dr</i>)

All of the PKR substrates above contained a C(4)-carbonyl group, and therefore we sought to determine the effect of modifying the C(4)-position. Thus, enyne **3.87** was

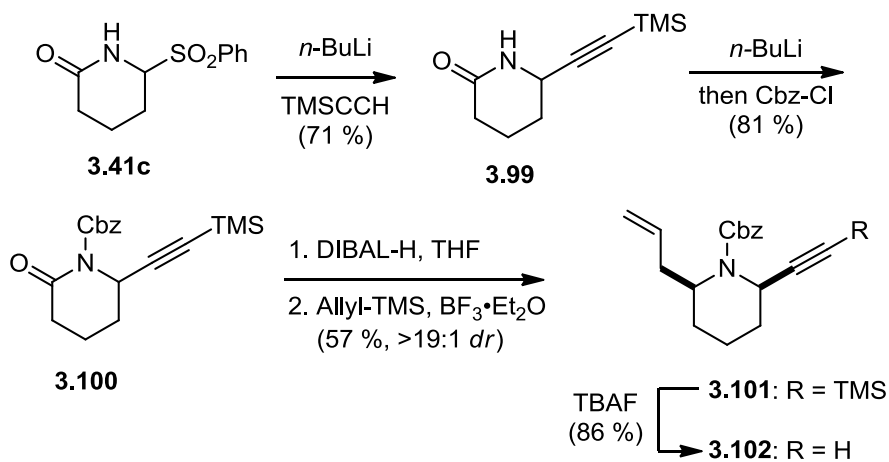
treated with L-selectride to deliver the alcohol **3.97**, which was protected as the corresponding TBS-ether **3.98** (Scheme 3.24).

Scheme 3.24



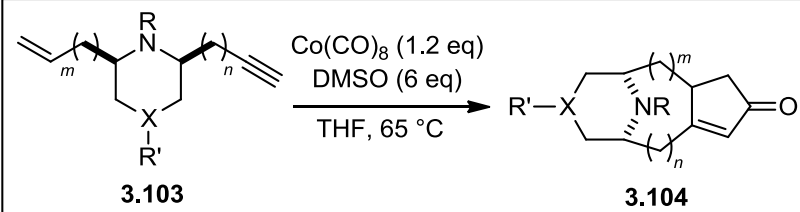
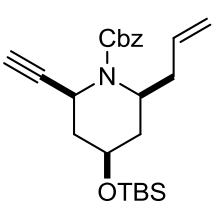
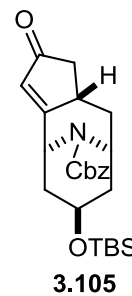
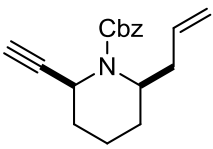
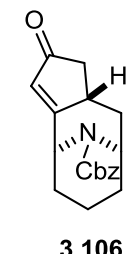
We also wanted to obtain an enyne bearing no functionality at the C(4)-position (Scheme 3.25). Thus, we resorted to a different strategy to prepare **3.102**, which was based on previous work in the group. Alkylation of the known amidosulphone **3.41c** with the acetylide derived from TMS-acetylene gave the lactam **3.99**, which was acylated to provide **3.100**. Reduction of the more electrophilic carbonyl group in **3.100** with DIBAL-H, followed by a Sakurai reaction gave the enyne **3.102** after cleavage of the silyl group from the acetylene moiety.

Scheme 3.25



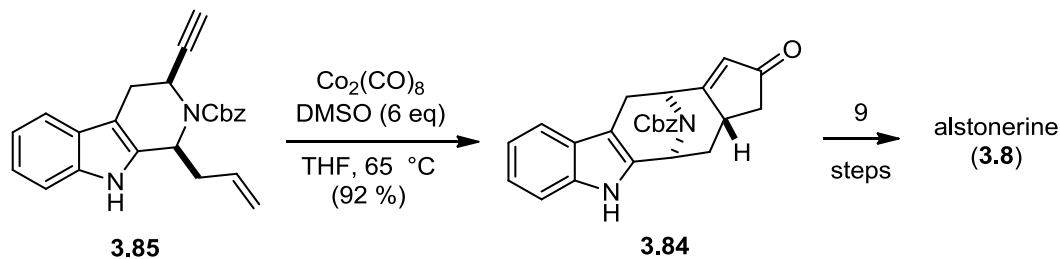
Subsequent study of the PKR strategy on these new substrates revealed that the substitution at C(4) in **3.12** had the potential to affect the diastereoselectivity of the PKR reaction (Table 3.2). The PKR of the silyl ether **3.98** gave **3.105** in good yield as a single diastereomer (entry 1). However, the substrate **3.102** containing a methylene group at C(4) underwent a PKR to give a mixture (4:1) of diastereomers in good yield favoring **3.106** (entry 2).

Table 3.2

<div style="text-align: center;">  </div>			
entry	substrate	product	yield
1	 <p style="text-align: center;">3.98</p>	 <p style="text-align: center;">3.105</p>	69 %
2	 <p style="text-align: center;">3.102</p>	 <p style="text-align: center;">3.106</p>	74 % (4:1 <i>dr</i>)

Our plan for the total synthesis of alstonerine (**3.8**) hinged on the PKR of the enyne **3.85** to give the BAzB cyclopentenone **3.84** (Scheme 3.26). Thus, following chemistry previously developed in our research group, the enyne **3.85** was prepared in four steps from L-tryptophan. The PKR of **3.85** proceeded smoothly to give the cyclopentenone **3.84** in excellent yield as a single diastereomer bearing the required stereochemical arrangement necessary for a total synthesis of alstonerine; in fact, the total synthesis was ultimately accomplished in an additional 9 steps from the PKR product **3.84**.

Scheme 3.26



3.2 RESULTS/DISCUSSION

3.2.1 Introduction

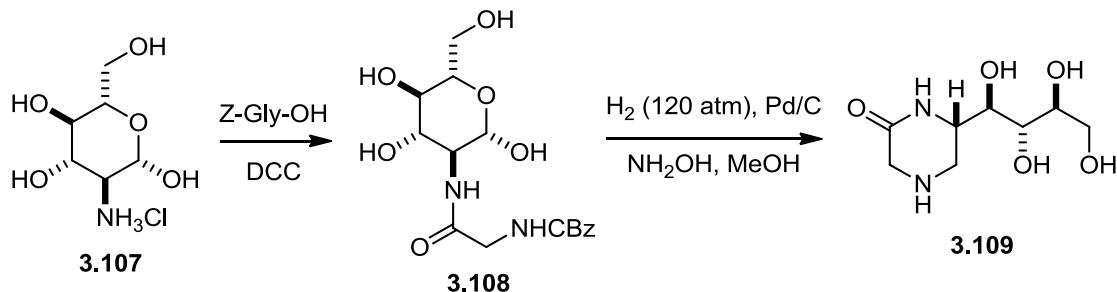
In the context of further studying the scope of the Pauson-Khand reaction, my role on the project was to develop a synthesis of 2,6-*cis*-disubstituted piperazines for application in the new methodology. Unlike the synthesis of piperadines, piperadones, and pyrrolidines bearing this type of substitution pattern, which have been thoroughly studied from a synthetic standpoint, the synthesis of 2,6-disubstituted piperazines lacked precedent at the time we set out. We thus had to investigate a number of different strategies to accomplish this goal.

3.2.2 Application of the Martin Group Pauson-Khand Method to Access Bridged Bicyclic Piperazines

We were initially interested in synthesizing chiral piperazine enyne substrates for use in the PKR reaction, and therefore we were attracted to a method reported by the Bols research group which used glucosamine (**3.107**) as a starting material for the synthesis of chiral piperazines.¹⁶⁹ Their approach called for an initial DCC coupling of glucosamine and N-Cbz-glycine to give **3.108** (Scheme 2.37). In our hands this reaction proved very difficult due to the highly polar nature of the coupled product, which made purification

very difficult. Bols reported that the product precipitated from the reaction mixture, however, the best we could do was the formation of a gelatinous substance, which proved to fine to be filtered from the reaction. We therefore decided to subject the crude product mixture to the next hydrogenolysis/reductive amination step to form piperazone **3.109** in the hopes that we could take advantage of the basic nitrogen during the isolation/purification. They reported the use to extremely high pressures of hydrogen gas (>250 atm) for this reaction, however, with our equipment the best we could achieve was 120 atm. It was not clear what the outcome of this reaction was, but due to very complicated mixtures we decided to turn our attention to a modified synthetic approach.

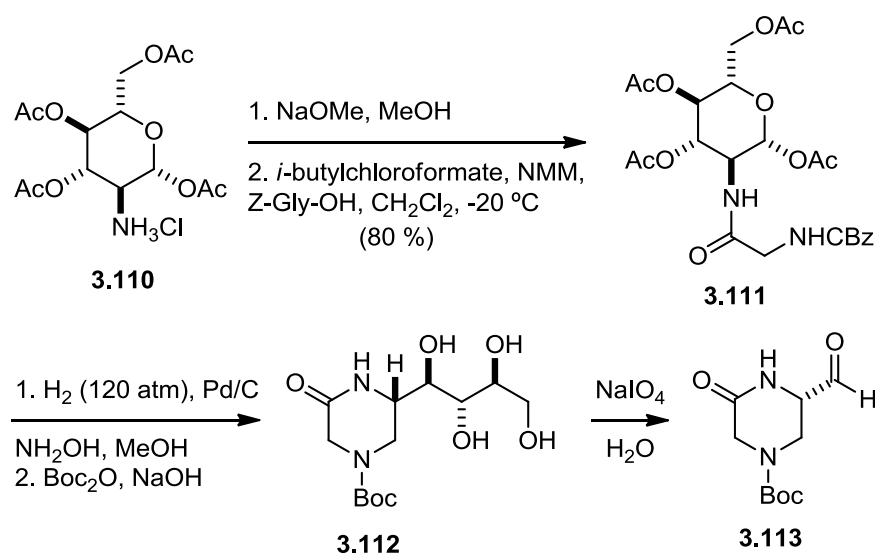
Scheme 3.27



We reasoned that peracylated glucosamine **3.110** would likely provide better material properties, and thus simplify the purification and isolation procedures (Scheme 3.28). We also wanted to remove the use of DCC as a coupling reagent for this sequence since the urea byproduct had been complicating the subsequent product mixtures. To that end, we reacted **3.110** with the preformed mixed anhydride of Z-Gly-OH , which provide excellent yields of the amide product **3.333**. We still found the subsequent hydrogenation to be troublesome in that complex mixtures were always observed. It is possible that our inability to achieve the prescribed 250 atm of hydrogen was to blame for the erratic results. In an attempt to access our targeted aldehyde **3.113**, we made an effort to carry

forward the crude product mixtures from the hydrogenation step. We first Boc-protected the amine, then subjected the crude material to a periodate cleavage. Analysis of the crude reaction by TLC, NMR, and MS revealed small quantities of the desired product (<10%), however, considering the difficulty and lack of efficiency of this sequence we decided to abandon our efforts to synthesize chiral material and move to a less complicated racemic approach.

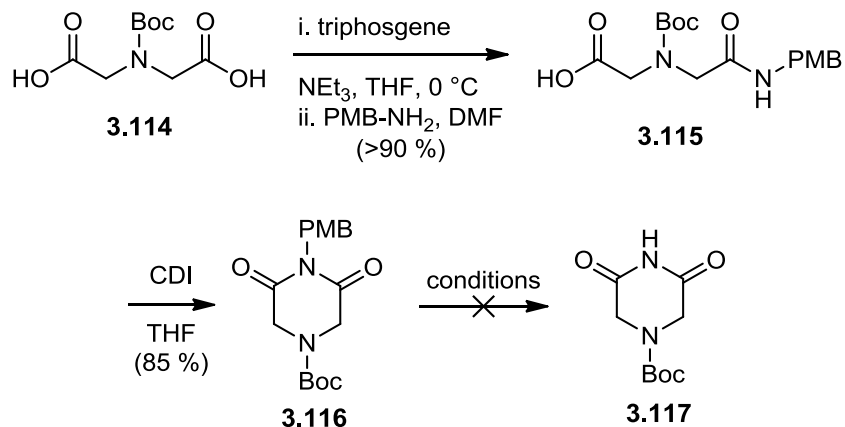
Scheme 3.28



We first looked to synthesize imide **3.117** with the idea in mind of borrowing from the chemistry developed in our group for accessing 2,6-*cis*-disubstituted piperadines, which relies on iterative Mannich reactions to install the 2,6-substituents (Scheme 3.29). Beginning with N-Boc-aminodiacetic acid **3.114**, we first formed an amide with triphosgene and *p*-methoxybenzylamine (PMB-NH₂) to provide **3.115** in >90% yield. Next a cyclization mediated by carbonyldiimidazole (CDI) was performed to provide the fully protected imide **3.116**. Unfortunately, all attempts to deprotect the imide nitrogen to give **3.117** failed in our hands. We explored various different

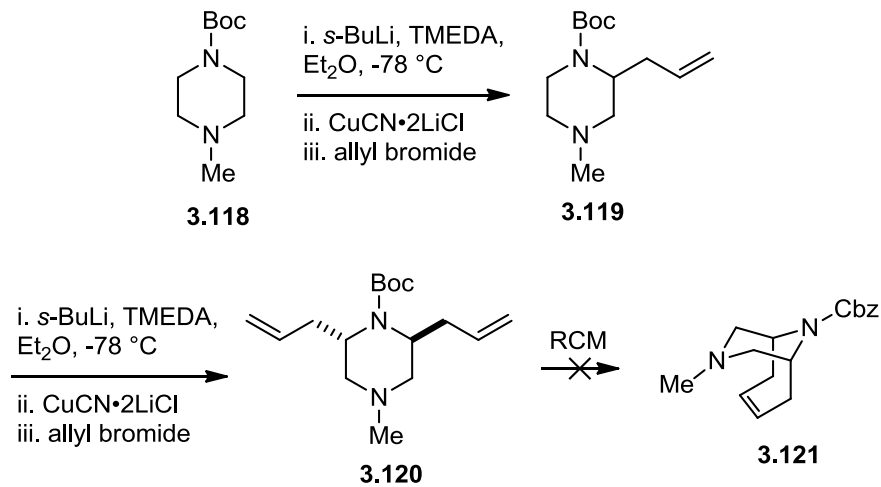
hydrogenolysis, Lewis acid mediate, and oxidative PMB-deprotection conditions; however, the PMB-imide proved more robust than we had anticipated and returned only starting material in most cases.

Scheme 3.29



We were next drawn to a procedure reported for the synthesis of 2-substituted piperazines, which utilized chemistry developed by the Beak group.^{170, 171} In this paper they managed to accomplish a number of alkylation reactions of organolithium reagents prepared from directed lithiation of Boc-protected piperazines. In only one example they attempted to take the mono-substituted piperazines and further substitute at the adjacent position. They claimed in their paper that they achieved the 2,6-*cis*-disubstitution, however, in attempting to repeat this chemistry we found that the *trans*-stereochemistry was in fact obtained. This was confirmed by failed attempts to perform an RCM reaction to provide the BAzB **3.121**.

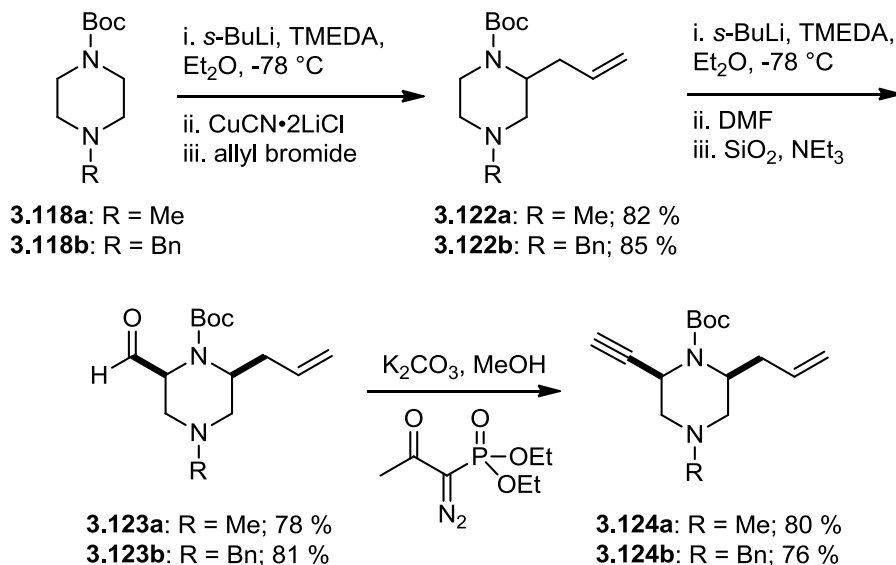
Scheme 3.30



Despite that fact that the *cis*-orientation was not directly accessible, we were cognizant of reports by Beak where formylation of the carbanions of 2-substituted piperazines furnished the 2,6-*trans*-formyl compounds.¹⁷¹ Beak had discovered that the formyl products of these types of reactions could efficiently be epimerized on silica gel to supply the 2,6-*cis*-stereochemistry. We therefore aimed to apply this type of approach to our targeted piperazine systems. The synthesis of both the N-Me and N-Bn piperazine enynes **3.124** started from the corresponding 1,4-diprotected piperazine compounds **3.118** (Scheme 3.31). The allylation of both compounds relied on the carbamate directed α -deprotonation using *sec*-butyllithium/TMEDA followed by transmetallation to the cuprate. The cuprate of these compounds readily undergoes alkylation with allyl bromide to afford compounds **3.122a-b** in 82% and 85% yields, respectively. The subsequent formylations of **3.122a-b** were also performed using *sec*-butyllithium/TMEDA, but without the need for an intermediate transmetallation. The initial product mixture obtained in these reactions are a mixture of the *cis*- and *trans*-isomers (with *trans* being the major product), but equilibration of the resulting mixture cleanly yields the more

thermodynamically stable *cis*-products **3.123a-b** in 78% and 81% yields. Alkynylation using the Bestmann-Ohira reagent produces enynes **3.124a-b** in 80% and 76% yields, which provided the desired PKR substrates.

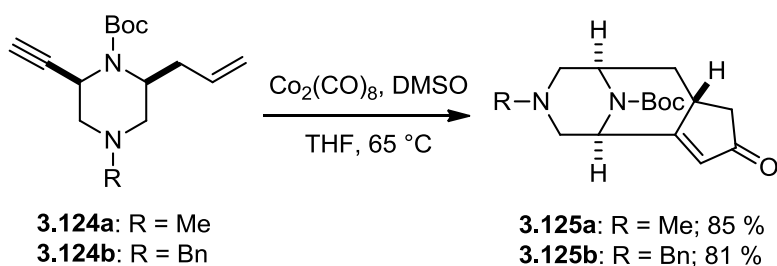
Scheme 3.31



With the piperazine enynes in hand, the use of the PKR for synthesizing the corresponding BAZB compounds could be investigated (Scheme 3.32). Initial results, following methods previously established in the group, provided a 53% yield of the azabicyclic **3.125a** starting from methylated piperazine **3.124a**. It was found that the loading of cobalt onto this particular alkyne was considerably slower than what had been observed with comparable piperazine substrates. Increasing the loading of the Co-complex from 1.1 molar equivalents to 1.5 molar equivalents, as well as heating the reaction during this time to 40 °C (as opposed to rt), dramatically increased the efficiency of the cobalt-alkyne complexation and the yield of **3.125a** increased to 85%. Subjecting the benzylated piperazine compound **3.124a** to the same conditions afforded **3.125b** in

81% yield. It is also important to note that the PKR products **3.125a-b** were both obtained as a single diastereomer. Based on the comparison of NMR data to previous examples (outlined in the Background section), we assigned the stereochemistry of these compounds to be the same as was observed in the previously established examples.

Scheme 3.32



3.3 CONCLUSION

With the synthesis of the piperazino substrates, the Martin group methodology for the synthesis of bridged azabicyclic molecules using the Pauson-Khand reaction was completed. It is noteworthy, that despite a lack of initial precedent, that the piperazine azabicycles **3.125a-b** were ultimately accessible in only four synthetic operations in ~42% overall yield.

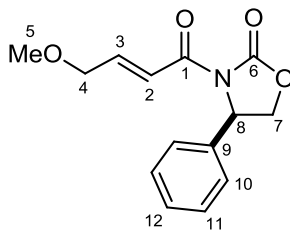
Chapter 4 – Experimental Procedures

4.1 GENERAL METHODS

Solvents and reagents were reagent grade and used without purification unless otherwise noted. Zn granules were activated by stirring with 1M HCl for 10 min, filtering, rinsing with D.I. H₂O, MeOH, then Et₂O, and drying under vacuum before use. MgO was dried by heating under vacuum at 140 °C overnight before use. Dichloromethane (CH₂Cl₂) and triethylamine (Et₃N) were distilled from calcium hydride and stored under nitrogen and methyl acetate was purified before each use by first drying over MgSO₄ and then distilling from P₂O₅. Tetrahydrofuran (THF) and diethyl ether (Et₂O) were passed through a column of neutral alumina and stored under argon. Methanol (MeOH) and dimethylformamide (DMF) were passed through a column of molecular sieves and stored under argon. Toluene was passed through a column of Q5 reactant and stored under argon. ¹H nuclear magnetic resonance (NMR) spectra were obtained at 500 or 400 MHz. Chemical shifts are reported in parts per million (ppm, δ) and referenced to the solvent. Coupling constants are reported in hertz (Hz). Spectral splitting patterns are designated as: s, singlet; d, doublet; t, triplet; m, multiplet; comp, overlapping multiplets of magnetically non-equivalent protons; br, broad; and bs, broad singlet. Infrared (IR) spectra were obtained using a Perkin-Elmer FTIR 1600 spectrophotometer on sodium chloride plates and reported as wavenumbers (cm⁻¹). Low-resolution chemical ionization mass spectra were obtained on a Finnigan TSQ-70 instrument, and high-resolution measurements were obtained on a VG Analytical ZAB2-E instrument. Analytical thin layer chromatography was performed using Merck 250 micron 60F-254 silica plates. The plates were visualized with UV light, *p*-anisaldehyde,

and potassium permanganate. Flash column chromatography was performed according to Still's method using ICN Silitech 32-63 D 60A silica gel.

4.2 EXPERIMENTALS

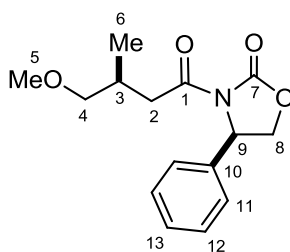


2.117

(4R)-3-[(2E)-4-Methoxybut-2-enoyl]-4-phenyl-1,3-oxazolidin-2-one (2.117).

Pivaloyl chloride (0.572 g, 4.74 mmol) was added dropwise to a solution of the acid **2.115** (0.500 g, 4.31 mmol) in THF (15 mL) at -20 °C. After 1 h, 4-(*R*)-phenyloxazolidinone (2.064 g, 12.6 mL) and LiCl (0.201 g, 4.74 mmol) were added in one portion, and the reaction was warmed to room temperature and stirred overnight. The reaction was diluted with H₂O (5 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layers were then washed sat. aq. NaHCO₃ (2 x 5 mL), brine (1 x 5 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with Hex/EtOAc (1:1) to give 0.983 g (87%) of **2.117** as a white solid: mp = 70-71 °C; ¹H NMR (CDCl₃, 300 MHz) δ 7.49 (ddd, *J* = 15.4, 2.0, 2.0 Hz, 1 H), 7.35 (comp, 5 H), 7.07 (ddd, *J* = 15.6, 4.4, 4.4 Hz, 1 H), 5.51 (dd, *J* = 8.7, 4.1 Hz, 1 H), 4.73 (dd, *J* = 8.7, 8.7 Hz, 1 H), 4.30 (dd, *J* = 8.7, 3.8 Hz, 1 H), 4.14 (dd, *J* = 4.6, 2.0 Hz, 2 H), 3.42 (s, 3 H); ¹³C NMR (CDCl₃, 300 MHz) δ 164.4, 153.8, 146.8, 139.3, 129.3, 128.8, 126.2, 120.4, 71.6, 70.2, 58.9, 57.9; MS (CI) *m/z* 261 [C₁₄H₁₅NO₄ (M) requires 261].

NMR Assignments. ^1H NMR (CDCl_3 , 300 MHz) δ 7.49 (ddd, $J = 15.4, 2.0, 2.0$ Hz, 1 H, C3-H), 7.35 (comp, 5 H, C10-H, C11-H, C12-H), 7.07 (ddd, $J = 15.6, 4.4, 4.4$ Hz, 1 H, C2-H), 5.51 (dd, $J = 8.7, 4.1$ Hz, 1 H, C7-H), 4.73 (dd, $J = 8.7, 8.7$ Hz, 1 H, C8-H), 4.30 (dd, $J = 8.7, 3.8$ Hz, 1 H, C7-H), 4.14 (dd, $J = 4.6, 2.0$ Hz, 2 H, C4-H), 3.42 (s, 3 H, C5-H); ^{13}C NMR (CDCl_3 , 300 MHz) δ 164.4 (C1), 153.8 (C6), 146.8 (C9), 139.3 (C3), 129.3 (C11), 128.8 (C12), 126.2 (C10), 120.4 (C2), 71.6 (C4), 70.2 (C7), 58.9 (C5), 57.9 (C8).



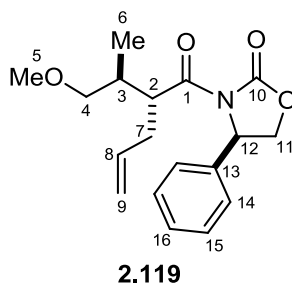
2.118

(4R)-3-[(3S)-4-Methoxy-3-methylbutanoyl]-4-phenyl-1,3-oxazolidin-2-one

(2.118). A solution of methyllithium (0.91 M in hexanes, 15.7 mL, 14.2 mmol) was added dropwise to a slurry of $(\text{CuI})_3(\text{Me}_2\text{S})_4$ (3.508 g, 14.8 mmol) in THF (63 mL) at -78°C in the dark. The mixture was stirred at -78°C for 20 min and iodotrimethylsilane (2 mL, 14.2 mmol, freshly distilled in the dark over copper powder under argon) was added dropwise. The resulting mixture was stirred in the dark for 10 min at -78°C , whereupon a solution of imide **2.117** (2.9769 g, 11.4 mmol) in THF (17 mL) was added dropwise. After 5 h, NEt_3 (7.9 mL, 57.0 mmol) was added dropwise, and stirring was continued for an additional 1 h at -78°C . The reaction was quenched conc. NH_4OH (5 mL) and sat. aq. NH_4Cl (5 mL) were added, and the reaction was warmed to room temperature. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 25 mL), then

the combined organic layers were washed with brine (25 mL), dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with hexanes/ethylacetate (4:1) to give 2.8723 g (91%) of **2.118** as a pale yellow crystalline solid: mp = 53-54 °C; ¹H NMR (CDCl₃, 400 MHz) δ 7.30 (comp, 4 H), 5.40 (dd, *J* = 8.5, 3.4 Hz, 1 H), 4.65 (dd, *J* = 12.0, 12.0 Hz, 1 H), 4.25 (dd, *J* = 8.9, 3.8 Hz, 1 H), 3.21 (s, 3 H), 3.08 (dd, *J* = 16.8, 5.8 Hz, 1 H), 2.72 (dd, *J* = 16.4, 7.9 Hz, 1 H), 2.30 (m, 1 H), 0.88 (d, *J* = 6.5 Hz, 3 H); ¹³C NMR (CDCl₃, 300 MHz) δ 172.2, 153.9, 129.3, 128.9, 126.2, 77.5, 70.1, 58.9, 57.8, 39.7, 30.1, 17.1.

NMR Assignments. ¹H NMR (CDCl₃, 400 MHz) δ 7.30 (comp, 4 H, C11-H, C12-H, C13-H), 5.40 (dd, *J* = 8.5, 3.4 Hz, 1 H, C8-H), 4.65 (dd, *J* = 12.0, 12.0 Hz, 1 H), 4.25 (dd, *J* = 8.9, 3.8 Hz, 1 H, C8-H), 3.21 (s, 3 H, C5-H), 3.08 (dd, *J* = 16.8, 5.8 Hz, 1 H, C4-H), 2.72 (dd, *J* = 16.4, 7.9 Hz, 1 H, C4-H), 2.30 (m, 1 H, C3-H), 0.88 (d, *J* = 6.5 Hz, 3 H, C6-H); ¹³C NMR (CDCl₃, 300 MHz): δ 172.2 (C1), 153.9 (C7), 129.3 (C12), 128.9 (C13), 126.2 (C11), 77.5 (C4), 70.1 (C8), 58.9 (C5), 57.8 (C9), 39.7 (C2), 30.1 (C3), 17.1 (C6).

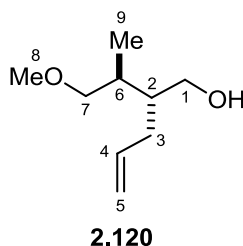


(4R)-3-[(2R)-2-[(2S)-1-Methoxypropan-2-yl]pent-4-enoyl]-4-phenyl-1,3-oxazolidin-2-one (2.119). A solution of *n*-BuLi (2.76 M in hexanes, 4.1 mL, 11 mmol) was added dropwise to a solution of hexamethyldisilazane (2.6 mL, 12 mmol) in THF (12 mL) at -78 °C, and the reaction was stirred for 20 min at -78 °C and then at 0 °C for 20

min. After returning to the -78 °C bath, a solution of imide **2.118** (2.872 g, 10.4 mmol) in THF (21 mL) was added dropwise via syringe. The reaction was stirred at -78 °C for 1 h, then between -45 °C and -35 °C for 20 min before returning to -78 °C and carrying out the dropwise addition of allyl iodide (2.8 mL, 31 mmol, freshly distilled in the dark over copper powder under argon). The reaction was stirred at -78 °C for 2 h, and then was transferred to a -45 °C bath. After maintaining the reaction temperature at -45 °C for 30 min, the reaction was allowed to gradually warm in a controlled manner to -10 °C over a 1 h period. The reaction was stirred at -10 °C for 3 h, then was quenched by the addition of saturated aqueous NH₄Cl (15 mL). EtOAc (30 mL) was added, the layers were separated. The aqueous layer was extracted with EtOAc (3 x 25 mL), and the combined organic layers were washed with brine (15 mL), dried (MgSO₄), filtered, and concentrated. The residue was purified by flash column chromatography eluting with hexanes/EtOAc (4:1) to give 2.284 g (69%) of **2.119** as a colorless oil: ¹H NMR (CDCl₃, 400 MHz) δ 7.30 (comp, 4 H), 5.56 (m, 1 H), 5.42 (dd, *J* = 8.9, 3.8 Hz, 1 H), 4.81 (dd, *J* = 16.4, 1.7 Hz, 1 H), 4.80 (d, *J* = 10.9 Hz), 4.63 (dd, *J* = 8.9, 8.9 Hz, 1 H), 4.23 (dd, *J* = 8.9, 3.4 Hz, 1 H), 4.09 (ddd, *J* = 9.4, 6.5, 4.8 Hz, 1 H), 3.34 (dd, *J* = 4.8, 2.7 Hz, 2 H), 3.29 (s, 3 H), 2.34 (ddd, *J* = 14.0, 14.0, 7.9 Hz, 1 H), 2.25 (ddd, *J* = 12.6, 12.6, 6.5 Hz, 1 H), 2.06 (m, 1 H), 1.01 (d, *J* = 6.8 Hz, 3 H); ¹³C NMR (CDCl₃, 300 MHz) δ 174.9, 153.9, 139.5, 135.2, 129.2, 128.8, 126.3, 117.3, 75.9, 69.8, 59.1, 58.1, 44.7, 36.0, 34.4, 15.2; LRMS (CI) *m/z* 318 [C₁₈H₂₃NO₄ (M + 1) requires 318].

NMR Assignments. ¹H NMR (CDCl₃, 400 MHz) δ 7.30 (comp, 4 H, C14-H, C15-H, C16-H), 5.56 (m, 1 H, C8-H), 5.42 (dd, *J* = 8.9, 3.8 Hz, 1 H, C11-H), 4.81 (dd, *J* = 16.4, 1.7 Hz, 1 H, C9-H), 4.80 (d, *J* = 10.9 Hz, 1 H, C9-H), 4.63 (dd, *J* = 8.9, 8.9 Hz, 1 H, C12-H), 4.23 (dd, *J* = 8.9, 3.4 Hz, 1 H, C11-H), 4.09 (ddd, *J* = 9.4, 6.5, 4.8 Hz, 1 H, C2-H), 3.34 (dd, *J* = 4.8, 2.7 Hz, 2 H, C4-H), 3.29 (s, 3 H, C5-H), 2.34 (ddd, *J* = 14.0,

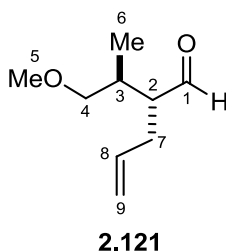
14.0, 7.9 Hz, 1 H, C7-H), 2.25 (ddd, $J = 12.6, 12.6, 6.5$ Hz, 1 H, C7-H), 2.06 (m, 1 H, C3-H), 1.01 (d, $J = 6.8$ Hz, 3 H, C6-H); ^{13}C NMR (CDCl_3 , 300 MHz) δ 174.9 (C1), 153.9 (C10), 139.5 (C13), 135.2 (C8), 129.2 (C14), 128.8 (C16), 126.3 (C14), 117.3 (C9), 75.9 (C4), 69.8 (C11), 59.1 (C5), 58.1 (C12), 44.7 (C2), 36.0 (C3), 34.4 (C7), 15.2 (C6).



(2R)-2-[(2S)-1-Methoxypropan-2-yl]pent-4-en-1-ol (2.120). A solution of the imide **2.119** (2.889 g, 9.11 mmol) in THF (91 mL) and H_2O (30 mL) was cooled to 0 °C and treated successively with H_2O_2 (30% in H_2O , 8.3 mL, 72.9 mmol) and a solution of $\text{LiOH}\cdot\text{H}_2\text{O}$ (0.764 g, 18.2 mmol). Once the addition was completed, the cooling bath was removed, and the reaction was stirred at room temperature for 9 h. At this point, the reaction was cooled to 0 °C, 1.5 M aq. $\text{Na}_2\text{S}_2\text{O}_3$ (100 mL) was added, and the mixture was stirred for 1 h. The THF was removed under reduced pressure and 15% aq. NaOH was added to adjust the pH to 12-13, whereupon the mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried (MgSO_4), filtered, and concentrated under reduced pressure to recover 1.226 g (82%) of the chiral auxilliary **2.173** as a white solid. The aqueous layer was then acidified to pH 1 with 6 M HCl, and then extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with brine (150 mL), dried (MgSO_4), filtered, and concentrated under reduced pressure. The crude carboxylic acid was dissolved in THF (8 mL) and added

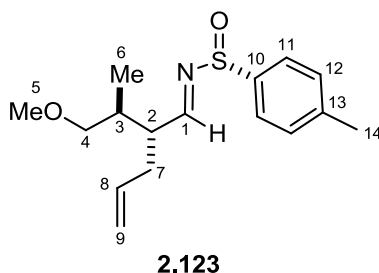
dropwise to a slurry of LiAlH_4 (0.519 g, 13.67 mmol) in THF (25 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 14 h. The reaction was quenched by the sequential careful addition of H_2O (14 mL), 15% aq. NaOH (14 mL), and H_2O (30 mL) and the mixture extracted with EtOAc (4 x 40 mL). The combined organic layers were washed with brine (1 x 40 mL), dried (MgSO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography eluting with Hex:EtOAc (3:2) to provide 1.311 g (91%) of alcohol **2.120** as a colorless oil: ^1H NMR (CDCl_3 , 300 MHz) δ 5.77 (app ddt, $J = 17.2$, 10.0, 6.9, 6.9 Hz, 1 H), 5.04 (dt, $J = 15.6$, 2.1 Hz, 1 H), 4.98 (dt, $J = 10.0$, 2.0 Hz, 1 H), 3.50 (app ddt, $J = 30.5$, 11.5, 11.5, 6.9 Hz, 2 H), 3.33 (s, 3 H), 3.30 (dddd, $J = 19.5$, 9.5, 9.5, 6.7 Hz, 2 H), 3.08 (br, 1 H), 2.14 – 1.90 (comp, 3 H), 1.74 – 1.64 (m, 1 H), 0.89 (d, $J = 7.2$ Hz, 3 H); ^{13}C NMR (CDCl_3 , 300 MHz) δ 137.7, 116.4, 76.7, 63.4, 59.1, 44.4, 35.6, 33.2, 13.6.

NMR Assignments. ^1H NMR (CDCl_3 , 300 MHz) δ 5.77 (app ddt, $J = 17.2$, 10.0, 6.9, 6.9 Hz, 1 H, C8-H), 5.04 (dt, $J = 15.6$, 2.1 Hz, 1 H, C9-H), 4.98 (dt, $J = 10.0$, 2.0 Hz, 1H, C9-H), 3.50 (app ddt, $J = 30.5$, 11.5, 11.5, 6.9 Hz, 2 H, C4-H), 3.33 (s, 3 H, C5-H), 3.30 (dddd, $J = 19.5$, 9.5, 9.5, 6.7 Hz, 2 H, C1-H), 3.08 (br, 1 H, OH), 2.14 – 1.90 (comp, 3 H, C7-H, C2-H), 1.74 – 1.64 (m, 1 H, C3-H), 0.89 (d, $J = 7.2$ Hz, 3 H, C6-H); ^{13}C NMR (CDCl_3 , 300 MHz) δ 137.7 (C8), 116.4 (C9), 76.7 (C4), 63.4 (C1), 59.1 (C5), 44.4 (C2), 35.6 (C3), 33.2 (C7), 13.6 (C6).



(2R)-2-[(2S)-1-Methoxypropan-2-yl]pent-4-enal (2.121). A solution of alcohol **2.120** (1.00 g, 6.32 mmol), PCC (2.04 g, 9.48 mmol) and SiO₂ (3 g) in CH₂Cl₂ (21 mL) was stirred at room temperature for 20 min. The reaction was filtered through a 2 inch pad of SiO₂ rinsing with CH₂Cl₂ (200 mL), and the filtrate and washings were concentrated under reduce pressure to provide 0.987 g (99%) of aldehyde **2.121** as a colorless oil: ¹H NMR (CDCl₃, 300 MHz) δ 9.64 (d, *J* = 2.0 Hz, 1 H), 5.73 (appt ddt, *J* = 13.6, 6.9, 3.3 Hz, 1 H), 5.05 (dd, *J* = 18.4, 1.5 Hz, 1 H), 4.98 (dt, *J* = 11.5, 1.3 Hz, 1 H), 3.28 (m, 2 H), 3.27 (s, 3 H), 2.42 (m, 1 H), 2.22 (m, 1 H), 0.94 (d, 3 H, *J* = 7.2 Hz); ¹³C NMR (CDCl₃, 300 MHz) δ 204.9, 136.1, 116.9, 75.5, 58.9, 53.5, 34.5, 30.1, 14.3.

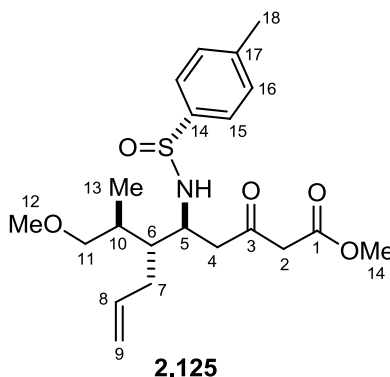
NMR Assignments. ¹H NMR (CDCl₃, 300 MHz) δ 9.64 (d, *J* = 2.0 Hz, 1 H, C1-H), 5.73 (appt ddt, *J* = 13.6, 6.9, 3.3 Hz, 1 H, C8-H), 5.05 (dd, *J* = 18.4, 1.5 Hz, 1 H, C9-H), 4.98 (dt, *J* = 11.5, 1.3 Hz, 1 H, C9-H), 3.28 (m, 2 H, C4-H), 3.27 (s, 3 H, C5-H), 2.42 (m, 1 H, C7-H), 2.22 (m, 1 H, C7-H), 0.94 (d, 3 H, *J* = 7.2 Hz, C6-H); ¹³C NMR (CDCl₃, 300 MHz) δ 204.9 (C1), 136.1 (C8), 116.9 (C9), 75.5 (C4), 58.9 (C5), 53.5 (C2), 34.5 (C3), 30.1 (C7), 14.3 (C6).



(*R*)-N-[(1*E*,2*R*)-2-[(2*S*)-1-Methoxypropan-2-yl]pent-4-en-1-ylidene]-4-methylbenzene-1-sulfinamide (2.123**).** To a solution of aldehyde **2.121** (0.158 g, 1.02 mmol) in THF (10 mL) were added (*R*)-*p*-toluenesulfinamide (0.204 g, 1.33 mmol) and Ti(OEt)₄ (0.53 mL, 2.5 mmol). The reaction was stirred at room temperature for 22 h, whereupon CH₂Cl₂ (60 mL) and H₂O (20 mL) were added, resulting in the formation of a white precipitate. The reaction mixture was filtered through a pad of Celite, and washed with CH₂Cl₂ (50 mL). The layers were separated, and the organic layer was dried (MgSO₄), filtered, and concentrated. The residue was purified by flash column chromatography in hexanes/EtOAc (7:1) to give 0.221 g (74%) of **2.123**: ¹H NMR (CDCl₃, 400 MHz) δ 8.16 (d, *J* = 6.5 Hz, 1 H), 7.53 (d, *J* = 8.2 Hz, 2 H), 7.28 (d, *J* = 8.5 Hz, 2 H), 5.63 (appt ddt, *J* = 17.1, 10.3, 6.8 Hz, 1 H), 4.99 (dd, *J* = 17.1, 1.7 Hz, 1 H), 4.92 (dd, *J* = 11.6, 1.7 Hz, 1 H), 3.32 (dd, *J* = 12.0, 5.8 Hz, 1 H), 3.30 (s, 3 H), 3.25 (dd, *J* = 9.6, 5.8 Hz, 1 H), 2.77 (m, 1 H), 2.39 (s, 3 H), 2.39 (m, 1 H), 2.28 (m, 1 H), 2.08 (m, 1 H), 0.88 (d, *J* = 7.2 Hz, 3 H); ¹³C NMR (CDCl₃, 400 MHz) δ 168.9, 142.2, 141.8, 135.7, 129.9, 124.8, 117.1, 75.9, 58.9, 46.4, 35.9, 33.7, 21.6, 13.5; MS (CI) *m/z* 294 [C₁₆H₂₃NO₂S (M + 1) requires 294].

NMR Assignments. ¹H NMR (CDCl₃, 400 MHz) δ 8.16 (d, *J* = 6.5 Hz, 1 H, C1-H), 7.53 (d, *J* = 8.2 Hz, 2 H, C11-H), 7.28 (d, *J* = 8.5 Hz, 2 H, C12-H), 5.63 (appt ddt, *J* = 17.1, 10.3, 6.8 Hz, 1 H, C8-H), 4.99 (dd, *J* = 17.1, 1.7 Hz, 1 H, C9-H), 4.92 (dd, *J* = 11.6, 1.7 Hz, 1 H, C9-H), 3.32 (dd, *J* = 12.0, 5.8 Hz, 1 H, C4-H), 3.30 (s, 3 H, C5-H),

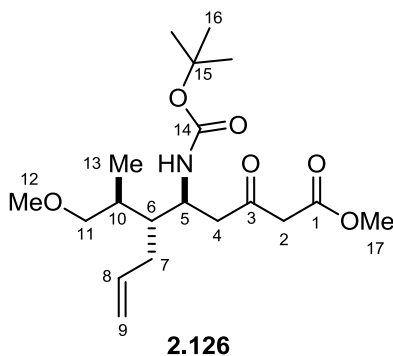
3.25 (dd, $J = 9.6, 5.8$ Hz, 1 H, C4-H), 2.77 (m, 1 H, C2-H), 2.39 (s, 3 H, C14-H), 2.39 (m, 1 H, C3-H), 2.28 (m, 1 H, C7-H), 2.08 (m, 1 H, C7-H), 0.88 (d, $J = 7.2$ Hz, 3 H, C6-H); ^{13}C NMR (CDCl_3 , 400 MHz) δ 168.9 (C1), 142.2 (C13), 141.8 (C8), 135.7 (C10), 129.9 (C11), 124.8 (C12), 117.1 (C9), 75.9 (C4), 58.9 (C5), 46.4 (C3), 35.9 (C7), 33.7 (C2), 21.6 (C14), 13.5 (C6).



Methyl (5*S*,6*R*)-6-[(2*S*)-1-methoxypropan-2-yl]-5-[(*R*)-(4-methylbenzene)sulfinyl]amino}-3-oxonon-8-enoate (2.125): A solution of methyl acetate (0.219 g, 2.95 mmol) in THF (2.5 mL) was added dropwise to a solution of NaHMDS (1.90 M in THF, 1.55 mL, 2.95 mmol) in THF (0.5 mL) at -78 °C. The reaction was stirred at -78 °C for 45 min, and then Et_2O (1 mL) followed by a solution of sulfinimide **2.123** (0.054 g, 0.17 mmol) in THF (0.5 mL) was added via syringe. The reaction was stirred at -78 °C for 3 h until the starting material was consumed by TLC (SiO_2 , 3:2 Hex:EtOAc) and the reaction was warmed to -20 °C overnight. The reaction was quenched with sat. aq. NH_4Cl (5 mL) and H_2O (1 mL), and then extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (1 x 5 mL), dried (MgSO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting in Hex:EtOAc (1:1) to provide 0.220 g

(91%) of **2.125** as a mixture (8:1) of diastereomers: ^1H NMR (CDCl_3 , 400 MHz) δ 7.53 (d, J = 8.2 Hz, 2 H), 7.29 (d, J = 7.9 Hz, 2 H), 5.77 (app ddt, J = 17.1, 9.9, 6.8, 6.8 Hz, 1 H), 5.05 (dd, J = 17.1, 1.7 Hz, 1 H), 4.97 (dd, J = 10.2, 1.7 Hz, 1 H), 4.95 (d, J = 8.5 Hz, 1 H), 3.85 (m, 1 H), 3.73 (s, 3 H), 3.50 (s, 2 H), 3.16 (d, J = 5.8 Hz, 2 H), 3.14 (s, 3 H), 3.09 (dd, J = 17.4, 5.1 Hz, 1 H), 2.94 (dd, J = 17.1, 5.5 Hz, 1 H), 2.40 (s, 3 H), 2.20 – 2.02 (comp, 2 H), 1.90 – 1.82 (m, 1 H), 1.78 – 1.70 (m, 1 H), 0.80 (d, J = 7.2 Hz, 3 H); LRMS (CI) m/z 410 [$\text{C}_{21}\text{H}_{31}\text{NO}_5\text{S}$ ($M + 1$) requires 410].

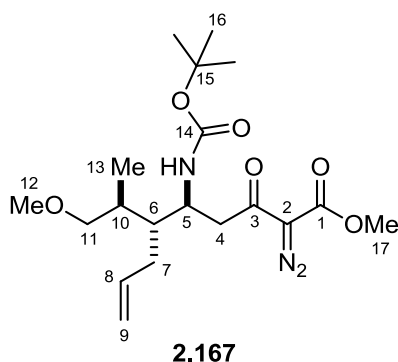
NMR Assignments. ^1H NMR (CDCl_3 , 400 MHz) δ 7.53 (d, J = 8.2 Hz, 2 H, C15-H), 7.29 (d, J = 7.9 Hz, 2 H, C16-H), 5.77 (app ddt, J = 17.1, 9.9, 6.8, 6.8 Hz, 1 H, C8-H), 5.05 (dd, J = 17.1, 1.7 Hz, 1 H, C9-H), 4.97 (dd, J = 10.2, 1.7 Hz, 1 H, C9-H), 4.95 (d, J = 8.5 Hz, 1 H, NH), 3.85 (m, 1 H, C5-H), 3.73 (s, 3 H, C19-H), 3.50 (s, 2 H, C2-H), 3.16 (d, J = 5.8 Hz, 2 H, C11-H), 3.14 (s, 3 H, C12-H), 3.09 (dd, J = 17.4, 5.1 Hz, 1 H, C4-H), 2.94 (dd, J = 17.1, 5.5 Hz, 1 H, C4-H), 2.40 (s, 3 H, C18-H), 2.20 – 2.02 (comp, 2 H, C7-H), 1.90 – 1.82 (m, 1 H, C10-H), 1.78 – 1.70 (m, 1 H, C6-H), 0.80 (d, J = 7.2 Hz, 3 H, C13-H).



Methyl (5*S*,6*R*)-5-[[*tert*-butoxy]carbonyl]amino}-6-[(2*S*)-1-methoxypropan-2-yl]-3-oxonon-8-enoate (2.126). A solution of the sulfinimide **2.125** (0.150 g, 0.366

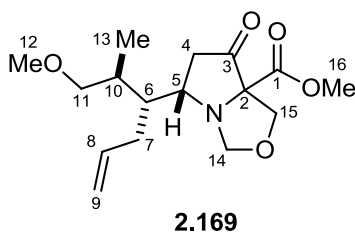
mmol) in MeOH (3.7 mL) was cooled to 0 °C, and TFA (0.14 mL, 1.83 mmol) was added. After stirring at 0 °C for 5 min, the cooling bath was removed, the reaction was stirred at room temperature for 2 h, and it was concentrated under reduced pressure. The residue was dissolved in THF (3.7 mL), and DMAP (0.004 g, 0.04 mmol), NEt₃ (0.15 mL, 1.10 mmol), and Boc₂O (0.11 mL, 0.475 mmol) were added. The reaction mixture was stirred at room temperature for 4 h, and sat. aq. NH₄Cl (1 mL) and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue was purified via flash column chromatography eluting with Hex:EtOAc (4:1) to give 0.069 g (51%) of **2.126** as a colorless oil: ¹HNMR (CDCl₃, 400 MHz, rotamers) δ 6.28 (br d, *J* = 8.4 Hz, 1 H), 5.84-5.73 (m, 1 H), 5.10-5.02 (comp, 2 H), 4.46 (bs, 1 H), 4.13-4.04 (m, 1 H), 3.71 (s, 3 H), 3.60-3.48 (m, 1 H), 3.35 (s, 2 H), 3.31-3.29 (m, 1 H), 3.26-3.16 (comp, 2 H), 2.81-2.67 (m, 1 H), 2.14-1.96 (comp, 2 H), 1.77-1.71 (m, 1 H), 1.46 (s, 3 H), 1.42 (s, 3 H), 0.92 (d, *J* = 7.2 Hz, 3 H); LRMS (CI) *m/z* 372 [C₁₉H₃₄NO₆ (M+1) requires 372].

NMR Assignments: ¹HNMR (CDCl₃, 400 MHz, rotamers) δ 6.28 (br d, *J* = 8.4 Hz, 1H), 5.84-5.73 (m, 1 H), 5.10-5.02 (comp, 2 H), 4.46 (bs, 1 H), 4.13-4.04 (m, 1 H), 3.71 (s, 3 H), 3.60-3.48 (m, 1 H), 3.35 (s, 2 H), 3.31-3.29 (m, 1 H), 3.26-3.16 (comp, 2 H), 2.81-2.67 (m, 1 H), 2.14-1.96 (comp, 2 H), 1.77-1.71 (m, 1 H), 1.46 (s, 3 H), 1.42 (s, 3 H), 0.92 (d, *J* = 7.2 Hz, 3 H)



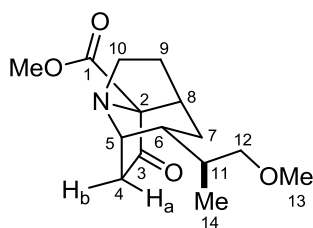
Methyl (5*S*,6*R*)-5-[(*tert*-butoxy)carbonyl]amino}-2-diazo-6-[(2*S*)-1-methoxypropan-2-yl]-3-oxonon-8-enoate (2.167). A solution of the **2.126** (0.326 g, 0.878 mmol) and *p*-acetamidobenzenesulfonyl azide (0.316 g, 1.32 mmol) in CH₃CN (2 mL) was cooled to 0 °C, whereupon NEt₃ (0.267 g, 2.63 mmol) was added. The reaction was stirred at 0 °C for 4 h and the reaction mixture was triturated with Et₂O (5 mL) and filtered, and the filtrant washed with Et₂O (5 mL). The filtrate and washings were concentrated and the crude residue was purified by column chromatography eluting with Hex/EtOAc (3:1) to give 0.328 g (94%) of **2.167** as a colorless oil: ¹HNMR (CDCl₃, 400 MHz, rotamers) δ 6.11 (br d, *J* = 9.2 Hz, 1 H), 5.86-5.74 (m, 1 H), 5.10-5.00 (comp, 2 H), 4.18-4.09 (m, 1 H), 3.84 (s, minor rotomer, 0.9 H), 3.83 (s, major rotomer, 2.1 H), 3.37-3.24 (comp, 4 H), 3.20-3.16 (m, 1 H), 3.10-3.05 (m, 1 H), 2.92-2.87 (m, 1 H), 2.12-2.02 (m, 1 H), 1.82-1.78 (m, 1 H), 1.40 (s, 3 H), 0.94 (d, *J* = 7.2 Hz, 3 H); LRMS (CI) *m/z* 398 [C₁₉H₃₂N₃O₆ (M+1) requires 398].

NMR Assignments. ¹HNMR (CDCl₃, 400 MHz, rotamers) δ 6.11 (br d, *J* = 9.2 Hz, 1 H), 5.86-5.74 (m, 1 H), 5.10-5.00 (comp, 2 H), 4.18-4.09 (m, 1 H), 3.84 (s, minor rotomer, 0.9 H), 3.83 (s, major rotomer, 2.1 H), 3.37-3.24 (comp, 4 H), 3.20-3.16 (m, 1 H), 3.10-3.05 (m, 1 H), 2.92-2.87 (m, 1 H), 2.12-2.02 (m, 1 H), 1.82-1.78 (m, 1 H), 1.40 (s, 3 H), 0.94 (d, *J* = 7.2 Hz, 3 H).



Methyl (5S)-5-[(2S,3R)-1-methoxy-2-methylhex-5-en-3-yl]-7-oxo-hexahydropyrrolo[1,2-c][1,3]oxazole-7a-carboxylate (2.169). A solution of the diazoester **2.167** (0.269 g, 0.677 mmol) in CH₂Cl₂ (14 mL) was stirred with Rh₂(OAc)₄ (0.015 g, 0.034 mmol) at room temperature overnight. The reaction was concentrated the crude residue purified by column chromatography eluting with Hex/EtOAc (4:1) to give 0.217 g (87%) of **2.168** as a mixture (1:1) of diastereomers, which was taken on crude. TFA (1.85 g, 16.26 mmol) was then added to a solution of the pyrrolidinone **2.168** (0.217 g, 0.588 mmol) and dimethoxymethane (1.12 g, 14.69 mmol) in CH₂Cl₂ (12 mL), and the reaction was stirred for 7 h at room temperature. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography eluting with Hex/EtOAc (2:1) to give 0.124 g (67%) of **2.169** as a mixture (1:1) of diastereomers as a colorless oil: ¹H NMR (CDCl₃, 400 MHz) δ 5.85 – 5.74 (m, 1 H), 5.10 – 4.99 (comp, 2 H), 4.72 (d, J = 7.2 Hz, 1 H), 4.21 (d, J = 7.2 Hz, 1 H), 4.13 (d, J = 9.2 Hz, 1 H), 4.05 (d, J = 8.9 Hz, 1 H), 3.77 (s, 3 H), 3.32 (s, 3 H), 3.38 – 3.22 (comp, 2 H), 2.66 (dd, J = 18.1, 9.9 Hz, 1 H), 2.60 – 2.56 (m, 1 H), 2.39 (dd, J = 17.8, 6.8 Hz, 1 H), 2.26 – 2.10 (m, 1 H), 2.06 – 1.94 (comp, 2 H, C7-H), 1.75 (dq, J = 6.8, 3.8 Hz, 1 H), 0.78 (d, J = 6.8 Hz, 3 H); ¹³C NMR (CDCl₃, 300 MHz) δ 209.2, 169.9, 138.2, 116.3, 87.3, 78.3, 76.1, 70.4, 59.0, 53.4, 46.3, 42.3, 40.8, 33.3, 30.8, 13.6; LRMS (CI) *m/z* 312 [C₁₆H₂₅NO₅ (M + 1) requires 312.17].

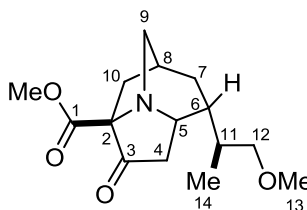
NMR Assignments. ^1H NMR (CDCl_3 , 400 MHz) δ 5.85 – 5.74 (m, 1 H, C8-H), 5.10 – 4.99 (comp, 2 H, C9-H), 4.72 (d, $J = 7.2$ Hz, 1 H, C14-H), 4.21 (d, $J = 7.2$ Hz, 1 H, C14-H), 4.13 (d, $J = 9.2$ Hz, 1 H, C15-H), 4.05 (d, $J = 8.9$ Hz, 1 H, C15-H), 3.77 (s, 3 H, C16-H), 3.32 (s, 3 H, C12-H), 3.38-3.22 (comp, 2 H, C11-H), 2.66 (dd, $J = 18.1, 9.9$ Hz, 1 H, C4-H), 2.60 – 2.56 (m, 1 H, C5-H), 2.39 (dd, $J = 17.8, 6.8$ Hz, 1 H, C4-H), 2.26 – 2.10 (m, 1 H, C7-H), 2.06 – 1.94 (comp, 2 H, C7-H, C10-H), 1.75 (dq, $J = 6.8, 3.8$ Hz, 1 H, C6-H), 0.78 (d, $J = 6.8$ Hz, 3 H, C13-H); ^{13}C NMR (CDCl_3 , 300 MHz) δ 209.2 (C3), 169.9 (C1), 138.2 (C8), 116.3 (C9), 87.3 (C2), 78.3 (C14), 76.1 (C11), 70.4 (C15), 59.0 (C16), 53.4 (C12), 46.3 (C4), 42.3 (C6), 40.8 (C5), 33.3 (C10), 30.8 (C7), 13.6 (C13).



2.171

Methyl 2-[(2*S*)-1-methoxypropan-2-yl]-9-oxo-7-azatricyclo[5.3.0.^{4,8}]decane-8-carboxylate (2.171). A solution of the oxazolidine **2.169** (0.010 g, 0.032 mmol) in toluene (2.5 mL) was stirred at 160 °C in a sealed tube for 3 h. After cooling to room temperature, the solvent was removed under reduced pressure, and the ^1H NMR of the crude mixture showed a 1:1 mixture of regioisomers **2.171** and **2.172**, which could be separated upon purification by flash column chromatography eluting with ethyl acetate to give 0.004 g (50%) **2.171** and 0.004 g (50%) **2.172**: ^1H NMR (C_6D_6 , 400 MHz) δ 3.36 (s, 3 H, C15-H), 3.32 (m, 1 H, C5-H), 3.00 (s, 3 H, C13-H), 2.96 (comp, 2 H, C10-H, C8-H), 2.79 (d, $J = 1.6$ Hz, 1 H, C12-H), 2.79 (s, 1 H), 2.75 (ddd, 1 H, $J = 13.5, 8.7, 5.6$ Hz, 1 H, C10-H), 2.46 (dd, $J = 17.6, 7.2$ Hz, 1 H, C4-H), 1.95 (d, $J = 17.6$ Hz, 1 H, C4-H),

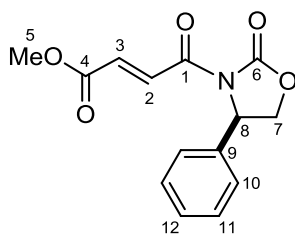
1.83 (ddd, $J = 17.2, 11.3, 5.9$ Hz, 1 H, C9-H), 1.55 (ddd, $J = 15.5, 9.5, 3.9$ Hz, 1 H, 1.33 (ddd, $J = 15.8, 9.9, 4.1$ Hz, 1 H), 1.21 (ddd, $J = 5.5, 3.6, 1.6$ Hz, 1 H), 1.12 (m, 1 H), 0.80 (m, 1 H, C11-H), 0.67 (d, $J = 6.8$ Hz, 3 H, C14-H).



2.172

Methyl (7S)-3-[(2S)-1-methoxypropan-2-yl]-6-oxo-8-azatricyclo[5.2.1.0^{4,8}]decane-7-carboxylate (2.172): ^1H NMR (C_6D_6 , 400 MHz) δ 3.75 (s, 3 H), 3.54 (dd, $J = 8.9, 6.2$ Hz, 1 H), 3.29 (s, 3 H), 3.25 – 3.17 (comp, 2 H), 2.88 (dd, $J = 15.7, 5.8$ Hz, 1 H), 2.84 – 2.80 (comp, 2 H), 2.70 (dd, $J = 14.0, 6.5$ Hz, 1 H), 2.45 – 2.40 (m, 1 H), 2.31 (d, $J = 15.7$ Hz, 1 H), 1.80 (d, $J = 14.3$, 1 H), 1.71 – 1.62 (comp, 2 H, C11-H), 1.52 (dd, $J = 13.7, 2.4$ Hz, 1 H), 1.32 – 1.24 (m, 1 H), 0.90 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (300 MHz) δ 210.9, 171.0, 78.7, 75.6, 59.0, 57.3, 57.2, 53.6, 49.9, 37.5, 37.3, 36.7, 34.0, 33.4, 15.2; MS (CI) m/z 282 [$\text{C}_{15}\text{H}_{23}\text{NO}_4$ ($M + 1$) requires 282.16].

NMR Assignments. ^1H NMR (400 MHz) δ 3.75 (s, 3 H, C15-H), 3.54 (dd, $J = 8.9, 6.2$ Hz, 1 H, C5-H), 3.29 (s, 3 H, C13-H), 3.25 – 3.17 (comp, 2 H, C12-H), 2.88 (dd, $J = 15.7, 5.8$ Hz, 1 H, C4-H), 2.84 – 2.80 (comp, 2 H, C9-H), 2.70 (dd, $J = 14.0, 6.5$ Hz, 1 H, C10-H), 2.45 – 2.40 (m, 1 H, C8-H), 2.31 (d, $J = 15.7$ Hz, 1 H, C4 H), 1.80 (d, $J = 14.3$, 1 H, C10-H), 1.71 – 1.62 (comp, 2 H, C11-H, C7-H), 1.52 (dd, $J = 13.7, 2.4$ Hz, 1 H, C7-H), 1.32 – 1.24 (m, 1 H, C6-H), 0.90 (d, $J = 6.8$ Hz, 3H, C14-H); ^{13}C NMR (300 MHz) δ 210.9 (C3), 171.0 (C1), 78.7 (C2), 75.6 (C12), 59.0 (C9), 57.3 (C13), 57.2 (C15), 53.6 (C4), 49.9 (C5), 37.5 (C6), 37.3 (C11), 36.7 (C8), 34.0 (C7), 33.4 (C10), 15.2 (C14).

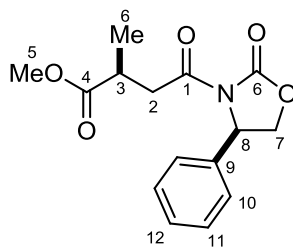


2.177

Methyl (2E)-4-oxo-4-[(4R)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]but-2-enoate (2.177). Triethylamine (1.9 mL, 13 mmol) and trimethylacetylchloride (1.6 mL, 12 mmol) were added sequentially dropwise with stirring to a solution of the acid **2.176** (1.47 g, 12.64 mmol) in THF (84 mL) at -78 °C. The reaction was stirred at -78 °C for 1 h, then at 0 °C for 1 h before being returned to -78 °C. In a separate flask, *n*-BuLi (2.48 M in hexanes, 5.11 mL, 12.6 mmol) was added dropwise to a solution of (*R*)-4-phenyloxazolidinone (2.064 g, 12.6 mmol) in THF (70 mL). After stirring for 20 min at -78 °C, this mixture was transferred via cannula to the solution of mixed anhydride reaction at -78 °C, and the flask which had contained deprotonated oxazolidinone was rinsed with 10 mL of THF. The reaction was stirred at -78 °C for 1 h, and then was allowed to slowly warm to RT and stir overnight. After 11 h the reaction was quenched by the addition of H₂O₂ (240 mL) and the layers were separated. Following extraction of the aqueous layer with EtOAc (3 x 100 mL), the combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with hexanes/ethyl acetate (1:1) to give 3.248 g (98%) of **2.177** as a white solid: mp = 92-94 °C; ¹H NMR (CDCl₃, 300 MHz) 8.17 (d, *J* = 15.2 Hz, 1 H), 7.43-7.31 (comp, 5 H), 6.87 (d, *J* = 15.2 Hz, 1 H), 5.50 (dd, *J* = 4.0, 10.4 Hz, 1 H), 4.76 (t, *J* = 8.8 Hz, 1 H), 4.35 (dd, *J* = 4.8, 8.0 Hz, 1 H), 3.81 (s, 3 H); ¹³C NMR (CDCl₃, 100 MHz) δ 165.1, 163.1, 153.2, 138.2, 138.2, 133.8, 132.2, 129.1, 128.8,

125.9, 70.2, 57.7, 52.2; IR (neat) 2934, 2859, 1781, 1728, 1690, 1387, 1342, 1307, 1196, 1172 cm^{-1} ; HRMS (CI) m/z 276.0869 [$\text{C}_{14}\text{H}_{14}\text{NO}_5$ ($M+1$) requires 276.0872].

NMR Assignments. ^1H NMR (CDCl_3 , 300 MHz) 8.17 (d, $J = 15.2$ Hz, 1 H, C2-H), 7.43-7.31 (comp, 5 H, C10-H, C11-H, C12-H), 6.87 (d, $J = 15.2$ Hz, 1 H, C3-H), 5.50 (dd, $J = 4.0, 10.4$ Hz, 1 H, C7-H), 4.76 (t, $J = 8.8$ Hz, 1 H, C8-H), 4.35 (dd, $J = 4.8, 8.0$ Hz, 1 H, C7-H), 3.81 (s, 3 H, C5-H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 165.1 (C4), 163.1 (C1), 153.2 (C6), 138.2 (C9), 133.8 (C2), 132.2 (C3), 129.1 (C11), 128.8 (C12), 125.9 (C10), 70.2 (C7), 57.7 (C5), 52.2 (C8).

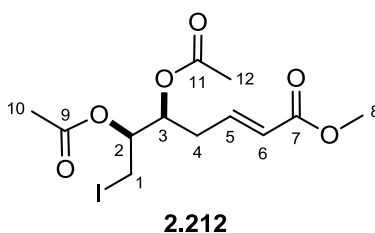


2.178

Methyl (2S)-2-methyl-4-oxo-4-[(4R)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]butanoate (2.178). A solution of methyllithium (0.91 M in hexanes, 15.7 mL, 14.2 mmol) was added dropwise to a slurry of $(\text{CuI})_3(\text{Me}_2\text{S})_4$ (3.508 g, 14.8 mmol) in THF (63 mL) at -78 $^\circ\text{C}$ in the dark. The mixture was stirred at -78 $^\circ\text{C}$ for 20 min and iodotrimethylsilane (2 mL, 14.2 mmol, freshly distilled in the dark over copper powder under argon) was added dropwise. The resulting mixture was stirred in the dark for 10 min at -78 $^\circ\text{C}$, whereupon a solution of imide **2.177** (2.9769 g, 11.4 mmol) in THF (16.8 mL) was added dropwise. Stirring was continued at -78 $^\circ\text{C}$ for 5 h, whereupon triethylamine (7.9 mL, 57.0 mmol) was added dropwise. After stirring for an additional 1 h at -78 $^\circ\text{C}$, saturated NH_4OH (5 mL) and saturated NH_4Cl (aq.) (5 mL) were added, and the reaction was removed from the cooling bath and allowed to warm to room

temperature and stirred for 20 min, forming a blue reaction mixture. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 25 mL), then the combined organic layers were washed with brine (25 mL), dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with Hex/EtOAc (4:1) to give 2.87 g (91%) of **2.178** as a white solid: mp = 53–54 °C; ¹H NMR (CDCl₃, 400 MHz) δ 7.40-7.26 (comp, 5 H), 5.43 (dd, *J* = 4.4, 8.0 Hz, 1 H), 4.72-4.68 (comp, 2 H), 4.24 (dd, *J* = 4.0, 8.8 Hz, 1 H), 3.54 (s, 3 H), 3.48-3.41 (m, 1 H), 3.24-3.15 (m, 1 H), 3.03-2.90 (comp, 2 H), 1.45 (t, *J* = 7.2 Hz, 1 H), 1.21 (d, *J* = 6.8 Hz, 3 H); ¹³C NMR (CDCl₃, 100 MHz) δ 175.3, 170.8, 153.6, 138.6, 128.9, 128.4, 125.5, 70.0, 57.3, 51.6, 46.2, 38.9, 34.9, 16.8, 8.5; LRMS (CI) *m/z* 292 [C₁₅H₁₈O₅ (M+1) requires 292].

NMR Assignments. ¹H NMR (CDCl₃, 400 MHz) δ 7.40-7.26 (comp, 5 H), 5.43 (dd, *J* = 4.4, 8.0 Hz, 1 H), 4.72-4.68 (comp, 2 H), 4.24 (dd, *J* = 4.0, 8.8 Hz, 1 H), 3.54 (s, 3 H), 3.48-3.41 (m, 1 H), 3.24-3.15 (m, 1 H), 3.03-2.90 (comp, 2 H), 1.45 (t, *J* = 7.2 Hz, 1 H), 1.21 (d, *J* = 6.8 Hz, 3 H); ¹³C NMR (CDCl₃, 100 MHz) δ 175.3, 170.8, 153.6, 138.6, 128.9, 128.4, 125.5, 70.0, 57.3, 51.6, 46.2, 38.9, 34.9, 16.8, 8.5.

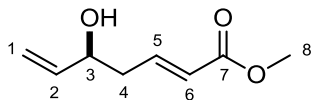


Methyl (2*E*,5*S*,6*S*)-5,6-bis(acetyloxy)-7-iodohept-2-enoate (2.212). A solution of 2-deoxy-D-ribose (25.0 g, 186.4 mmol) and methyl (triphenylphosphoranylidene) acetate (74.8 g, 223.6 mmol) in THF (750 mL) was heated under reflux for 6 h and then

cooled to room temperature. Imidazole (25.4 g, 372.7 mmol), PPh₃ (53.8 g, 205 mmol), and I₂ (54.4 g, 214.3 mmol) were then added sequentially to the reaction, and the mixture was stirred overnight in the dark at room temperature. The reaction was quenched with 10% aq. Na₂S₂O₃ (500 mL) and diluted with EtOAc (250 mL). The resulting layers were separated and the aq. layer extracted with CH₂Cl₂ (2 x 150 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated. The crude residue was dissolved in CH₂Cl₂ (375 mL), and then acetic anhydride (57.1 g, 559.1 mmol, 52.9 mL), DMAP (2.28 g, 18.7 mmol), and pyridine (44.2 g, 559.1 mmol, 45.2 mL) were added and the reaction was stirred at room temperature for 3 h. The reaction was then poured into a separatory funnel, and washed with 1 M aq. HCl (2 x 35 mL), saturated aqueous NaHCO₃ (1 x 35 mL), dried (MgSO₄), filtered and concentrated under reduced pressure. Trituration of the residue with Hex:Et₂O (100 mL, 8:1) precipitated out the Ph₃P=O byproduct formed during the olefination step. The precipitate was removed by filtration, and rinsed with Hex:Et₂O (150 mL, 8:1). The filtrate was then concentrated, redissolved in Et₂O (100 mL), and vacuum filtered through a 2.5 inch pad of SiO₂ using a 3 inch diameter fritted funnel. Once the initial filtrate had adsorbed onto the silica, the silica pad was rinsed with Et₂O (3 x 100 mL). The combined filtrate and washings were concentrated to give 62.3 g (87%) of **2.212** as a light yellow oil: ¹H NMR (CDCl₃, 400 MHz) δ 6.89-6.81 (m, 1H), 5.88 (dt, *J* = 15.6, 1.2 Hz, 1H), 5.18-5.14 (m, 1H), 5.00-4.96 (m, 1H), 3.73 (s, 3H), 3.38-3.23 (m, 2H), 2.61-2.47 (m, 2H), 2.12 (s, 3H), 2.07 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 169.50, 169.45, 165.9, 142.4, 123.9, 72.1, 71.5, 51.4, 32.4, 20.6, 2.1; IR (neat) 2952, 1747, 1660, 1436, 1372, 1223, 1040 cm⁻¹; HRMS (ESI) *m/z* 406.9962 [C₁₂H₁₇INaO₆ (M+Na) requires 406.9962].

NMR Assignments. ¹H NMR (CDCl₃, 400 MHz) δ 6.89-6.81 (m, 1H, C5-H), 5.88 (dt, *J* = 15.6, 1.2 Hz, 1H, C6-H), 5.18-5.14 (m, 1H, C2-H), 5.00-4.96 (m, 1H, C3-

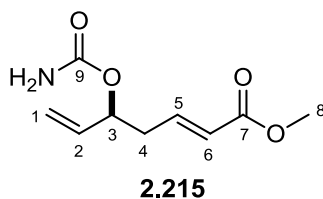
H), 3.73 (s, 3H, C8-H), 3.38-3.23 (m, 2H, C1-H), 2.61-2.47 (m, 2H, C4-H), 2.12 (s, 3H, C10-H), 2.07 (s, 3H, C12-H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 169.50 (C9), 169.45 (C11), 165.9 (C7), 142.4 (C5), 123.9 (C6), 72.1 (C2), 71.5 (C3), 51.4 (C8), 32.4 (C4), 20.63 (C12), 20.61 (C10), 2.1 (C1)



2.195

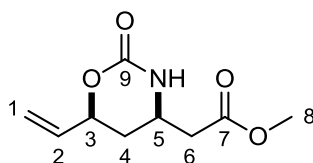
Methyl (2*E*,5*S*)-5-hydroxyhepta-2,6-dienoate (2.195). A mixture of **2.212** (62.3 g, 162.2 mmol) and freshly activated Zn granules (53.0 g, 810.9 mmol) in anhydrous MeOH (635 mL) was heated under reflux for 16 h. After cooling the reaction to room temperature, the suspension was filtered through a pad of Celite then rinsed with MeOH (190 mL). The combined filtrate and washings were concentrated and the crude residue was purified by flash chromatography eluting with Hex:EtOAc (2:1) to give 15.7 g (62%) of **2.195** as a colorless oil: ^1H NMR (CDCl_3 , 400 MHz) δ 7.01-6.93 (m, 1H), 5.94-5.84 (comp, 2H), 5.27 (dt, $J = 17.6, 1.2$ Hz, 1H), 5.15 (dt, $J = 10.4, 1.2$ Hz, 1H), 4.27 (q, $J = 6.0$ Hz, 1H), 3.72 (s, 3H), 2.72 (br s, 1H), 2.45 (td, $J = 7.2, 1.6$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 166.8, 145.0, 139.7, 123.3, 115.3, 71.3, 51.4, 39.7; IR (neat) 3428, 2951, 1722, 1660, 1436 cm^{-1} ; HRMS (CI) m/z 157.0864 [$\text{C}_8\text{H}_{13}\text{O}_3$ (M+1) requires 157.0865].

NMR Assignments. ^1H NMR (CDCl_3 , 400 MHz) δ 7.01-6.93 (m, 1H, C5-H), 5.94-5.84 (comp, 2H, C6-H and C2-H), 5.27 (dt, $J = 17.6, 1.2$ Hz, 1H, C1- H_a), 5.15 (dt, $J = 10.4, 1.2$ Hz, 1H, C1- H_b), 4.27 (q, $J = 6.0$ Hz, 1H, C3-H), 3.72 (s, 3H, C8-H), 2.72 (br s, 1H, OH), 2.45 (td, $J = 7.2, 1.6$ Hz, 2H, C4-H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 166.8 (C7), 145.0 (C5), 139.7 (C2), 123.3 (C6), 115.3 (C1), 71.3 (C3), 51.4 (C8), 39.7 (C4).



Methyl (2*E*,5*S*)-5-(carbamoyloxy)hepta-2,6-dienoate (2.215). Chlorosulfonyl isocyanate (15.70 g, 110.5 mmol) was added dropwise to solution of **2.195** (15.70 g, 100.5 mmol) in CH₂Cl₂ (1000 mL) at 0 °C. The reaction was warmed to room temperature and stirred for 1 h, at which time H₂O (300 mL) was added. The reaction flask was then equipped with a short-path distillation apparatus and heated to 60 °C (bath temp) until all of the CH₂Cl₂ had distilled. The remaining aqueous mixture was extracted with EtOAc (3 x 25 mL), and the combined organic layers were washed with sat. aq. NaHCO₃ (1 x 25 mL), brine (1 x 25 mL), dried (Na₂SO₄), filtered, and concentrated to give 20.25 g (99%) of **2.215** as a light yellow oil: ¹H NMR (CDCl₃, 400 MHz) δ 6.90 (dt, *J* = 15.6, 7.2, 1 H), 5.90 (dt, *J* = 15.6, 1.2 Hz, 1 H), 5.80 (ddd, *J* = 16.8, 10.8, 6.4 Hz, 1 H), 5.33-5.20 (comp, 3 H), 4.94 (br s, 1 H), 3.74 (s, 3 H), 2.62-2.49 (comp, 2 H); ¹³C NMR (CDCl₃, 100 MHz) δ 166.5, 156.1, 143.4, 135.4, 123.8, 117.2, 73.3, 51.5, 36.9; IR (neat) 3474, 3364, 3203, 2953, 2925, 1714, 1660, 1604, 1438, 1384, 1320, 1041 cm⁻¹; HRMS (CI) *m/z* 200.0925 [C₉H₁₄NO₄ (M+H) requires 200.0923].

NMR Assignments. ¹H NMR (CDCl₃, 400 MHz) δ 6.90 (dt, *J* = 15.6, 7.2, 1 H, C5-H), 5.90 (dt, *J* = 15.6, 1.2 Hz, 1 H, C6-H), 5.80 (ddd, *J* = 16.8, 10.8, 6.4 Hz, 1 H, C2-H), 5.33-5.20 (comp, 3 H, C1-H & C3-H), 4.94 (br s, 2 H, NH₂), 3.74 (s, 3 H, C8-H), 2.62-2.49 (comp, 2 H, C4-H_a & C4-H_b); ¹³C NMR (CDCl₃, 100 MHz) δ 166.5 (C9), 156.1 (C7), 143.4 (C5), 135.4 (C2), 123.8 (C6), 117.2 (C1), 73.3 (C3), 51.5 (C8), 36.9 (C4).

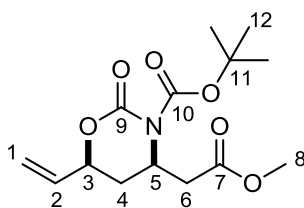


2.194

Methyl 2-[(4*R*,6*S*)-6-ethenyl-2-oxo-1,3-oxazinan-4-yl]acetate (2.194).

Compound **2.215** (20.25 g, 101.5 mmol) was dissolved in dry CH₂Cl₂ (895 mL) and cooled to -10 °C (bath temperature) in an ice/brine bath. NaH (4.31 g, 180.1 mmol, 60% *w/w* dispersion in mineral oil) was added in one portion, and the mixture was stirred under an atmosphere of N₂ (g) at -10 °C for 1.5 h. The reaction was quenched by the slow addition of saturated aqueous NH₄Cl (650 mL), and the aqueous layer was extracted with CH₂Cl₂ (4 x 300 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated under reduced pressure. The crude residue was then purified by recrystallization from methyl *tert*-butylether to give 17.09 g (85%) of **2.194** as a crystalline mixture (*dr* = 8:1) of diastereomers: ¹H NMR (CDCl₃, 400 MHz, major diastereomer) δ 6.48 (br s, 1H), 5.92-5.83 (m, 1H), 5.41 (d, *J* = 17.2 Hz, 1H), 5.27 (d, *J* = 10.8 Hz, 1H), 4.75 (q, *J* = 5.6 Hz, 1H), 3.98-3.91 (m, 1H), 3.72 (s, 3H), 2.57 (dd, *J* = 4.4, 3.2 Hz, 2H), 1.60-1.51 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ 170.8, 153.8, 134.7, 117.4, 76.6, 51.9, 47.0, 39.9, 33.1; IR (neat) 3428, 2951, 1722, 1660, 1436 cm⁻¹; HRMS (CI) *m/z* 200.0924 [C₉H₁₄NO₄ (M+H) requires 200.0923].

NMR Assignments. ¹H NMR (CDCl₃, 400 MHz) δ 6.48 (br s, 1H, NH), 5.92-5.83 (m, 1H, C2-H), 5.41 (d, *J* = 17.2 Hz, 1H, C1-H_a), 5.27 (d, *J* = 10.8 Hz, 1H, C1-H_b), 4.75 (q, *J* = 5.6 Hz, 1H, C3-H), 3.98-3.91 (m, 1H, C5-H), 3.72 (s, 3H, C8-H), 2.57 (dd, *J* = 4.4, 3.2 Hz, 2H, C6-H), 1.60-1.51 (m, 2H, C4-H); ¹³C NMR (CDCl₃, 100 MHz) δ 170.8 (C7), 153.8 (C9), 134.7 (C2), 117.4 (C1), 76.6 (C3), 51.9 (C8), 47.0 (C5), 39.9 (C4), 33.1 (C6).

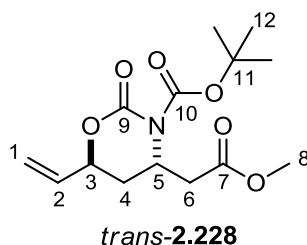


2.228

***tert*-Butyl (4*R*,6*S*)-6-ethenyl-4-(2-methoxy-2-oxoethyl)-2-oxo-1,3-oxazinane-3-carboxylate (2.228).** A solution of **2.194** (17.09 g, 85.45 mmol), Boc₂O (37.4 g, 170.9 mmol), NEt₃ (26.0 g, 256.9 mmol, 258.1 mL), and DMAP (1.03 g, 8.55 mmol) in CH₂Cl₂ (430 mL) was stirred at room temperature overnight. The reaction was quenched with 1 M HCl (340 mL), and the layers were separated. The aqueous layer was then extracted with CH₂Cl₂ (2 x 500 mL), and the combined organic layers were dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes:EtOAc (3:1) to give 22.22 g (87%) of **2.228** as a colorless oil: ¹H NMR (CDCl₃, 400 MHz) δ 5.82 (ddd, *J* = 17.0, 11.0, 6.0 Hz, 1H), 5.38 (d, *J* = 17.2 Hz, 1H), 5.26 (d, *J* = 10.8 Hz, 1H), 4.67-4.61 (m, 1H), 4.48 (ddd, *J* = 17.8, 9.0, 2.8 Hz, 1H), 3.66 (s, 3H), 2.92 (dd, *J* = 16.2, 3.2 Hz, 1H), 2.57 (dd, *J* = 16.6, 8.8 Hz, 1H), 2.54-2.48 (m, 1H), 2.74 (ddd, *J* = 14.0, 11.6, 9.2 Hz, 1H), 1.49 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 170.5, 151.9, 150.6, 133.4, 118.3, 83.7, 76.0, 51.8, 50.3, 40.0, 34.8, 27.9; IR (neat) 2982, 2955, 1792, 1759, 1736, 1438, 1393, 1370, 1307, 1160 cm⁻¹; HRMS (CI) 300.1453 [C₁₄H₂₂NO₆ (M+H) requires 300.1447].

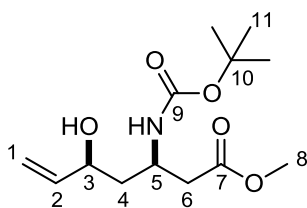
NMR Assignments. ¹H NMR (CDCl₃, 400 MHz) δ 5.82 (ddd, *J* = 6.0, 11.0, 17.0 Hz, 1H, C2-H), 5.38 (d, *J* = 17.2 Hz, 1H, C1-H_a), 5.26 (d, *J* = 10.8 Hz, 1H, C1-H_b), 4.67-4.61 (m, 1H, C3-H), 4.48 (ddd, *J* = 17.8, 9.0, 2.8 Hz, 1H, C5-H), 3.66 (s, 3H, C8-H), 2.92 (dd, *J* = 16.2, 3.2 Hz, 1H, C6-H_a), 2.57 (dd, *J* = 16.6, 8.8 Hz, 1H, C6-H_b), 2.54-2.48 (m, 1H, C4-H_a), 2.74 (ddd, *J* = 14.0, 11.6, 9.2 Hz, 1H, C4-H_b), 1.49 (s, 9H, C12-H); ¹³C

NMR (CDCl₃, 100 MHz) δ 170.5 (C9), 151.9 (C10), 150.6 (C7), 133.4 (C2), 118.3 (C1), 83.7 (C5), 76.0 (C3), 51.8 (C11), 50.3 (C8), 40.0 (C4), 34.8 (C6), 27.9 (C12).



Minor diastereomer: ¹H NMR (CDCl₃, 400 MHz) δ 5.87 (ddd, J = 17.2, 10.6, 6.0 Hz, 1 H), 5.41 (d, J = 17.6 Hz, 1 H), 5.30 (d, J = 10.4 Hz, 1 H), 4.93-4.87 (m, 1 H), 4.67 (ddd, J = 14.1, 6.0, 3.6 Hz, 1 H), 3.72 (s, 3H), 2.86 (dd, J = 15.8, 3.6 Hz, 1 H), 2.65 (dd, J = 16.0, 10.0 Hz, 1 H), 2.19 (app dt, J = 14.4, 3.2 Hz, 1 H), 2.08 (ddd, J = 14.6, 10.0, 5.2 Hz, 1 H), 1.54 (s, 9 H); ¹³C NMR (CDCl₃, 100 MHz) δ 170.4, 151.6, 148.5, 134.4, 117.9, 84.2, 74.9, 52.0, 49.6, 37.7, 31.2, 27.8.

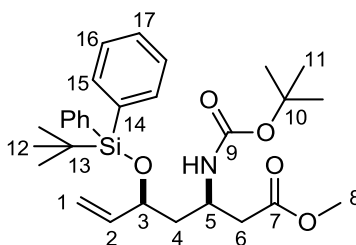
NMR Assignments. ¹H NMR (CDCl₃, 400 MHz) δ 5.87 (ddd, J = 17.2, 10.6, 6.0 Hz, 1 H, C2-H), 5.41 (d, J = 17.6 Hz, 1 H, C1-H_a), 5.30 (d, J = 10.4 Hz, 1 H, C1-H_b), 4.93-4.87 (m, 1 H, C3-H), 4.67 (ddd, J = 14.1, 6.0, 3.6 Hz, 1 H, C5-H), 3.72 (s, 3 H, C8-H), 2.86 (dd, J = 15.8, 3.6 Hz, 1 H, C6-H_a), 2.65 (dd, J = 16.0, 10.0 Hz, 1 H, C6-H_b), 2.19 (app dt, J = 14.4, 3.2 Hz, 1 H, C4-H_a), 2.08 (ddd, J = 14.6, 10.0, 5.2 Hz, 1 H, C4-H_b), 1.54 (s, 9 H, C12-H); ¹³C NMR (CDCl₃, 100 MHz) δ 170.4 (C9), 151.6 (C10), 148.5 (C7), 134.4 (C2), 117.9 (C1), 84.2 (C5), 74.9 (C3), 52.0 (C11), 49.6 (C8), 37.7 (C4), 31.2 (C6), 27.8 (C12).



2.229

Methyl (3*R*,5*S*)-3-[[*tert*-butoxy]carbonyl]amino}-5-hydroxyhept-6-enoate (2.229). A solution of **2.228** (22.22 g, 74.2 mmol) and Cs₂CO₃ (2.86 g, 14.8 mmol) in MeOH (370 mL) was stirred at room temperature for 24-48 h until starting material was consumed by TLC (SiO₂, Hex:EtOAc, 1:1). The reaction was then concentrated under reduced pressure to provide 20.28 g of crude **2.229** as a colorless oil that was taken on without further purification: ¹H NMR (CDCl₃, 400 MHz) δ 5.82 (ddd, *J* = 17.0, 11.0, 6.0 Hz, 1 H), 5.38 (d, *J* = 17.2 Hz, 1 H), 5.26 (d, *J* = 10.8 Hz, 1 H), 4.67-4.61 (m, 1 H), 4.48 (ddd, *J* = 17.8, 9.0, 2.8 Hz, 1 H), 3.66 (s, 3 H), 2.92 (dd, *J* = 16.2, 3.2 Hz, 1 H), 2.57 (dd, *J* = 16.6, 8.8 Hz, 1 H), 2.54-2.48 (m, 1 H), 2.74 (ddd, *J* = 14.0, 11.6, 9.2 Hz, 1 H), 1.49 (s, 9 H); ¹³C NMR (CDCl₃, 100 MHz) δ 170.5, 151.9, 150.6, 133.4, 118.3, 83.7, 76.0, 51.8, 50.3, 40.0, 34.8, 27.9; IR (neat) 2982, 2955, 1792, 1759, 1736, 1438, 1393, 1370, 1307, 1160 cm⁻¹; HRMS (CI) 300.1453 [C₁₄H₂₂NO₆ (M+H) requires 300.1447].

NMR Assignments. ¹H NMR (CDCl₃, 400 MHz) δ 5.82 (ddd, *J* = 6.0, 11.0, 17.0 Hz, 1 H, C2-H), 5.38 (d, *J* = 17.2 Hz, 1 H, C1-H_a), 5.26 (d, *J* = 10.8 Hz, 1 H, C1-H_b), 4.67-4.61 (m, 1 H, C3-H), 4.48 (ddd, *J* = 17.8, 9.0, 2.8 Hz, 1 H, C5-H), 3.66 (s, 3 H, C8-H), 2.92 (dd, *J* = 16.2, 3.2 Hz, 1 H, C6-H_a), 2.57 (dd, *J* = 16.6, 8.8 Hz, 1 H, C6-H_b), 2.54-2.48 (m, 1 H, C4-H_a), 2.74 (ddd, *J* = 14.0, 11.6, 9.2 Hz, 1 H, C4-H_b), 1.49 (s, 9 H, C12-H); ¹³C NMR (CDCl₃, 100 MHz) δ 170.5 (C9), 151.9 (C10), 150.6 (C7), 133.4 (C2), 118.3 (C1), 83.7 (C5), 76.0 (C3), 51.8 (C11), 50.3 (C8), 40.0 (C4), 34.8 (C6), 27.9 (C12).

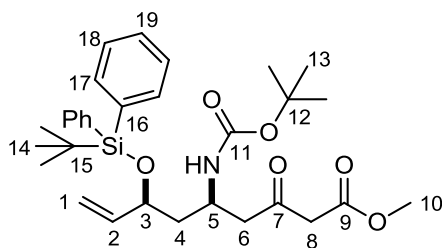


2.259

Methyl (3*R*,5*S*)-3-[[*tert*-butoxy]carbonyl]amino}-5-[[*tert*-butyldiphenylsilyl]oxy]hept-6-enoate (2.259). A solution of crude **2.229** (20.28 g, 74.2 mmol) from the previous step in DMF (50 mL) was added to a solution of TBDPS-Cl (-30.59 g, 111.3 mmol), imidazole (6.57 g, 96.46 mmol), and DMAP (0.091 g, 0.742 mmol) in DMF (320 mL), and the reaction was stirred at room temperature overnight. The reaction was quenched with 1 M HCl (300 mL), and the layers were separated. The aqueous layer was extracted with Et₂O (3 x 150 mL), and the combined organic layers were dried (MgSO₄), filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes:EtOAc (5:1) to give 30.38 g (80%) of **2.259** as a colorless oil: ¹H NMR (CDCl₃, 400 MHz, rotamers) δ 7.70-7.63 (comp, 4 H), 7.47-7.33 (comp, 6 H), 5.85 (ddd, *J* = 17.2, 10.2, 6.4 Hz, 1 H), 5.10-5.03 (comp, 2 H), 4.41 (app d, *J* = 8.8 Hz, 1 H), 4.17 (app q, *J* = 6.0 Hz, 1 H), 3.91-3.81 (m, 1 H), 3.60 (s, 3 H), 2.40 (app d, *J* = 4.8 Hz, 2 H), 1.62 (app t, *J* = 6.4 Hz, 2 H), 1.36 (s, 9 H), 1.07 (s, 9 H); ¹³C NMR (CDCl₃, 100 MHz, rotamers) δ 171.8, 154.8, 139.4, 135.90, 135.87, 134.1, 133.7, 129.8, 129.6, 127.6, 127.4, 115.5, 79.0, 72.2, 51.5, 44.2, 42.3, 39.6, 28.3, 27.0, 19.2; IR (neat) 3423, 2959, 2932, 2858, 1737, 1716, 1502, 1170, 1111 cm⁻¹; HRMS (ESI) 512.2830 [C₂₉H₄₂NO₅Si (M+H) requires 512.2754].

NMR Assignments. ¹H NMR (CDCl₃, 400 MHz, rotamers) δ 7.70-7.63 (comp, 4 H), 7.47-7.33 (comp, 6 H), 5.85 (ddd, *J* = 17.2, 10.2, 6.4 Hz, 1 H), 5.10-5.03 (comp, 2

H), 4.41 (app d, $J = 8.8$ Hz, 1 H), 4.17 (app q, $J = 6.0$ Hz, 1 H), 3.91-3.81 (m, 1 H), 3.60 (s, 3 H), 2.40 (app d, $J = 4.8$ Hz, 2 H), 1.62 (app t, $J = 6.4$ Hz, 2 H), 1.36 (s, 9 H), 1.07 (s, 9 H); ^{13}C NMR (CDCl_3 , 100 MHz, rotamers) δ 171.8, 154.8, 139.4, 135.90, 135.87, 134.1, 133.7, 129.8, 129.6, 127.6, 127.4, 115.5, 79.0, 72.2, 51.5, 44.2, 42.3, 39.6, 28.3, 27.0, 19.2.

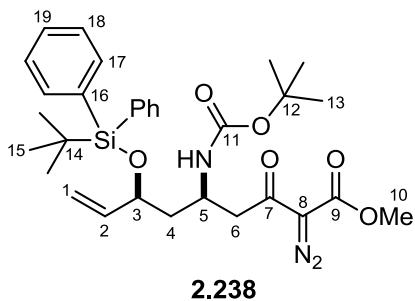


2.260

Methyl (5*R*,7*S*)-5-[[*(tert*-butoxy)carbonyl]amino]-7-[[*(tert*-butyldiphenylsilyl)oxy]-3-oxonon-8-enoate (2.260). A solution of freshly distilled methyl acetate (4.75 g, 64.10 mmol) in THF (128 mL) was added dropwise via syringe pump to a solution of NaHMDS (83.33 mmol, 1.8 M in hexane) in THF (167 mL) at -78 °C. After 30 min, a solution of **2.259** (3.28 g, 6.41 mmol) in THF (13 mL) was added dropwise to the reaction via syringe pump. During the syringe pump additions the metal needle used to transfer the substrate solutions was passed through a -78 °C bath to precool the solutions before introduction into the reaction flask. After 1 h at -78 °C, the reaction was warmed to -10 °C (ice/brine bath) and stirred for 6 h. The reaction was then quenched by addition of saturated aqueous NH_4Cl (300 mL) and warmed to room temperature. The reaction mixture was extracted with EtOAc (5 x 100 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with

hexanes:EtOAc (using a gradient from 9:1 to 5:1) to give 3.55 g (75%) of **2.260** as a colorless oil along with 0.56 g (17%) of recovered starting material: ^1H NMR (CDCl_3 , 400 MHz, rotamers) δ 7.69-7.62 (comp, 4 H), 7.47-7.33 (comp, 6 H), 5.83 (ddd, $J = 17.1$, 10.4, 6.4 Hz, 1 H), 5.10-5.03 (comp, 2 H), 4.37 (app d, $J = 8.0$ Hz, 1 H), 4.15 (app q, $J = 4.0$ Hz, 1 H), 3.92-3.83 (m, 1 H), 3.70 (s, 3 H), 3.37 (s, 2 H), 2.61 (app d, $J = 2.8$ Hz, 2 H), 1.68-1.61 (m, 2 H), 1.35 (s, 9 H), 1.07 (s, 9 H); ^{13}C NMR (CDCl_3 , 100 MHz, rotamers) δ 172.6, 167.6, 154.9, 139.4, 135.9, 135.8, 134.0, 133.6, 129.8, 129.6, 127.6, 127.4, 115.5, 79.0, 72.3, 52.2, 49.0, 47.9, 43.9, 42.1, 28.2, 26.9, 19.1; IR (neat) 3417, 2957, 2932, 2858, 1746, 1715, 1714, 1502, 1246, 1169, 1111 cm^{-1} ; HRMS (ESI) 576.2750 [$\text{C}_{31}\text{H}_{43}\text{NO}_6\text{SiNa}$ ($\text{M}+\text{Na}$) requires 576.2757].

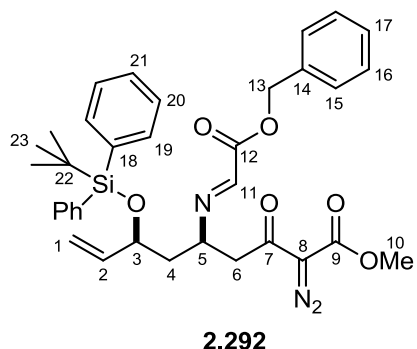
NMR Assignments. ^1H NMR (CDCl_3 , 400 MHz, rotamers) δ 7.69-7.62 (comp, 4 H), 7.47-7.33 (comp, 6 H), 5.83 (ddd, $J = 17.1$, 10.4, 6.4 Hz, 1 H), 5.10-5.03 (comp, 2 H), 4.37 (app d, $J = 8.0$ Hz, 1 H), 4.15 (app q, $J = 4.0$ Hz, 1 H), 3.92-3.83 (m, 1 H), 3.70 (s, 3 H), 3.37 (s, 2 H), 2.61 (app d, $J = 2.8$ Hz, 2 H), 1.68-1.61 (m, 2 H), 1.35 (s, 9 H), 1.07 (s, 9 H); ^{13}C NMR (CDCl_3 , 100 MHz, rotamers) δ 172.6, 167.6, 154.9, 139.4, 135.9, 135.8, 134.0, 133.6, 129.8, 129.6, 127.6, 127.4, 115.5, 79.0, 72.3, 52.2, 49.0, 47.9, 43.9, 42.1, 28.2, 26.9, 19.1



Methyl (5*R*,7*S*)-5-[(*tert*-butoxy)carbonyl]amino}-7-[(*tert*-butyldiphenylsilyl)oxy]-2-diazo-3-oxonon-8-enoate (2.238**).** A solution of **2.260** (3.55

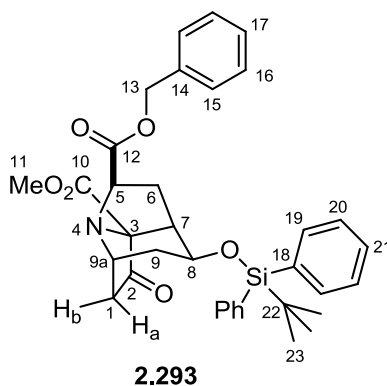
g, 1.97 mmol), *p*-ABSA (0.708 g, 2.95 mmol), and NEt₃ (0.598 g, 5.91 mmol) in MeCN (6.6 mL) was stirred at room temperature for 16 h. The reaction was then concentrated and the crude residue was triturated with Et₂O (25 mL). The precipitate was filtered and rinsed with Et₂O/CH₂Cl₂ (25 mL, 2:1), and the combined filtrate and washings were concentrated under reduced pressure. The crude residue was purified by column chromatography eluting with Hex:EtOAc (2:1) to give 1.14 g (92%) of **2.238** as a yellow oil: ¹H NMR (CDCl₃, 400 MHz, rotamers) δ 7.71-7.63 (comp, 4 H), 7.46-7.33 (comp, 6 H), 5.83 (ddd, *J* = 17.0, 10.2, 6.4 Hz, 1 H), 5.10-5.03 (comp, 2 H), 4.31 (app d, *J* = 9.6 Hz, 1 H), 4.21-4.13 (m, 1 H), 3.99-3.92 (m, 1 H), 3.81 (s, 3 H), 2.96-2.83 (comp, 2 H), 1.71-1.56 (comp, 2 H), 1.34 (s, 9 H), 1.06 (s, 9 H); ¹³C NMR (CDCl₃, 100 MHz, rotamers) δ 190.6, 161.6, 154.9, 139.4, 135.9, 134.1, 133.7, 129.7, 129.6, 128.2, 127.5, 127.4, 115.4, 78.8, 76.2, 72.2, 52.1, 45.6, 44.5, 42.7, 28.2, 26.9, 19.1; IR (neat) 3417, 2959, 2932, 2856, 2136, 1716, 1655, 1500, 1313, 1171, 1112 cm⁻¹; HRMS (ESI) 580.2838 [C₃₁H₄₂N₃O₆Si (M+H) requires 580.2843].

NMR Assignments. ¹H NMR (CDCl₃, 400 MHz, rotamers) δ 7.71-7.63 (comp, 4 H), 7.46-7.33 (comp, 6 H), 5.83 (ddd, *J* = 17.0, 10.2, 6.4 Hz, 1 H), 5.10-5.03 (comp, 2 H), 4.31 (app d, *J* = 9.6 Hz, 1 H), 4.21-4.13 (m, 1 H), 3.99-3.92 (m, 1 H), 3.81 (s, 3 H), 2.96-2.83 (comp, 2 H), 1.71-1.56 (comp, 2 H), 1.34 (s, 9 H), 1.06 (s, 9 H); ¹³C NMR (CDCl₃, 100 MHz, rotamers) δ 190.6, 161.6, 154.9, 139.4, 135.9, 134.1, 133.7, 129.7, 129.6, 128.2, 127.5, 127.4, 115.4, 78.8, 76.2, 72.2, 52.1, 45.6, 44.5, 42.7, 28.2, 26.9, 19.1.



Methyl (5*R*,7*S*)-5-[(*E*)-[2-(benzyloxy)-2-oxoethylidene]amino]-7-[(*tert*-butyldiphenylsilyl)oxy]-2-diazo-3-oxonon-8-enoate (2.292). Trifluoroacetic acid (0.315 g, 2.76 mmol) was added to a precooled solution of **2.238** (0.160 g, 0.276 mmol) in CH₂Cl₂ (1.5 mL) at 0 °C. The reaction was then warmed to room temperature and stirred for 2 h. The reaction was then concentrated to dryness and pumped down under high vacuum for 2 h to ensure the removal of all excess TFA. 4 Å molecular sieves (0.100 g) were added to a solution of the crude residue in CH₂Cl₂ (1.5 mL) and the mixture was cooled to 0 °C. NEt₃ (0.028 g, 0.276 mmol) was then added dropwise, and upon completion of the addition, the reaction was warmed to room temperature. A 1 M solution of benzyl glyoxylate (0.068 g, 0.414 mmol) in toluene was then added, and the reaction was stirred for 12 h at room temperature. The reaction mixture was then passed through a short pad of oven dried basic alumina, rinsing with CH₂Cl₂ (10 mL), and the combined filtrate and washings were concentrated under reduced pressure to give 0.173 g (>99%) of **2.292** as a colorless oil: ¹H NMR (CDCl₃, 400 MHz) δ 7.66 (s, 1 H), 7.63-7.59 (comp, 4 H), 7.39-7.28 (comp, 11 H), 5.75-5.67 (m, 1 H), 5.27 (s, 2 H), 4.93 (app d, *J* = 10.4 Hz, 1 H), 4.84 (app d, *J* = 17.2 Hz, 1 H), 4.10-4.05 (m, 1 H), 4.04-3.96 (m, 1 H), 3.79 (s, 3 H), 3.31 (dd, *J* = 18.0, 9.2 Hz, 1 H), 2.82 (dd, *J* = 16.0, 3.6 Hz, 1 H), 1.95-1.88 (m, 1 H), 1.84-1.77 (m, 1 H), 1.04 (s, 9 H).

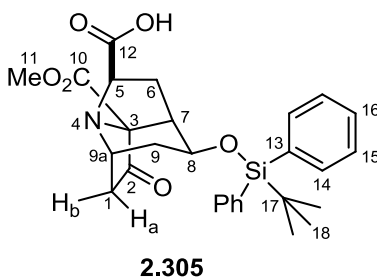
NMR Assignments. ^1H NMR (CDCl_3 , 400 MHz) δ 7.66 (s, 1 H, C11-H), 7.63-7.59 (comp, 4 H, Ar-H), 7.39-7.28 (comp, 11 H, Ar-H), 5.75-5.67 (m, 1 H, C2-H), 5.27 (s, 2 H, C13-H), 4.93 (app d, $J = 10.4$ Hz, 1 H, C1-H), 4.84 (app d, $J = 17.2$ Hz, 1 H, C1-H), 4.10-4.05 (m, 1 H, C3-H), 4.04-3.96 (m, 1 H, C5-H), 3.79 (s, 3 H, C10-H), 3.31 (dd, $J = 18.0, 9.2$ Hz, 1 H, C6-H), 2.82 (dd, $J = 16.0, 3.6$ Hz, 1 H, C6-H), 1.95-1.88 (m, 1 H, C4-H), 1.84-1.77 (m, 1 H, C4-H), 1.04 (s, 9 H, C16-H).



6-Benzyl-8-methyl-(6R)-3-[(*tert*-butyldiphenylsilyl)oxy]-9-oxo-7-azatricyclo[5.3.0.0^{4,8}]decane-6,8-dicarboxylate (2.293). Trifluoroacetic acid (1.36 g, 11.94 mmol) was added to a precooled solution of **2.238** (0.692 g, 1.19 mmol) in CH_2Cl_2 (6 mL) at 0 °C. The reaction was warmed to room temperature and stirred for 2 h. The reaction was then concentrated to dryness and pumped down under high vacuum for 2 h to ensure the removal of all excess TFA. 4 Å molecular sieves (0.600 g) were added to a solution of the crude residue in CH_2Cl_2 (6 mL) and the mixture was cooled to 0 °C. NEt_3 (0.132 g, 1.31 mmol) was then added dropwise, and upon complete of the addition, the reaction was warmed to room temperature. A 1 M solution of benzyl glyoxylate (0.293 g, 1.79 mmol) in toluene was then added, and the reaction was stirred for 16 h at room temperature. The reaction was filtered through Celite and rinsed with CH_2Cl_2 (6 mL) to

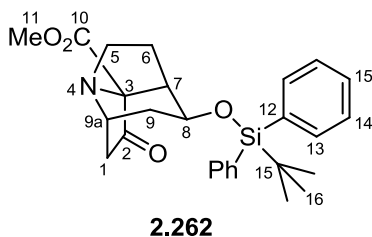
give **2.292** as a colorless oil along with an equimolar amount of $\text{NEt}_3 \cdot \text{TFA}$. The crude residue was dissolved in xylenes (24 mL), $\text{Rh}_2(\text{OAc})_4$ (0.026 g, 0.0595 mmol) was added, and the mixture was heated under reflux for 24 h. The reaction was concentrated to under reduced pressure, and the crude residue was purified by column chromatography eluting with Hex:EtOAc (3:1, with 1% v/v NEt_3) to give 0.462 g (65%) of **2.293** as a light yellow oil: ^1H NMR (CDCl_3 , 400 MHz) δ 7.59-7.55 (comp, 4 H), 7.45-7.35 (comp, 11 H), 5.28 (d, $J = 3.2$ Hz, 2 H), 4.15 (app q, $J = 6.0$ Hz, 1 H), 4.08-4.04 (m, 1 H), 3.94-3.89 (m, 1 H), 3.72 (s, 3 H), 2.96 (app q, $J = 3.2$ Hz, 1 H), 2.68 (dd, $J = 13.6, 5.6$ Hz, 1 H), 2.61 (dd, $J = 16.0, 6.4$ Hz, 1 H), 2.15-2.07 (m, 1 H), 1.80 (d, $J = 17.6$ Hz, 1 H), 1.35-1.19 (comp, 2 H), 1.04 (s, 9 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 207.0, 172.5, 169.7, 167.4, 135.5, 135.5, 135.3, 134.7, 133.5, 133.0, 130.0, 129.9, 128.6, 128.5, 127.8, 127.6, 82.4, 67.0, 66.2, 62.3, 54.2, 53.1, 49.7, 44.0, 33.6, 27.0, 26.8, 19.0; IR (neat) 2953, 2857, 1738, 1741, 1428, 1228, 1112 cm^{-1} ; HRMS (ESI) m/z 598.2614 [$\text{C}_{35}\text{H}_{40}\text{NO}_6\text{Si}$ (M+H) requires 598.2625].

NMR Assignments. ^1H NMR (CDCl_3 , 400 MHz) δ 7.59-7.55 (comp, 4 H, Ar-H), 7.45-7.35 (comp, 11 H, Ar-H), 5.28 (d, $J = 3.2$ Hz, 2 H, C13-H), 4.15 (app q, $J = 6.0$ Hz, 1 H, C5-H), 4.08-4.04 (m, 1 H, C8-H), 3.94-3.89 (m, 1 H, C9a-H), 3.72 (s, 3 H, C11-H), 2.96 (app q, $J = 3.2$ Hz, 1 H, C7-H), 2.68 (dd, $J = 13.6, 5.6$ Hz, 1 H, C6-H), 2.61 (dd, $J = 16.0, 6.4$ Hz, 1 H, C6-H), 2.15-2.07 (m, 1 H, C1-H_b), 1.80 (d, $J = 17.6$ Hz, 1 H, C1-H_a), 1.35-1.19 (comp, 2 H, C9-H), 1.04 (s, 9 H, C16-H).



(6*R*)-3-[(*tert*-Butyldiphenylsilyl)oxy]-8-(methoxycarbonyl)-9-oxo-7-azatricyclo [5.3.0.0^{4,8}]decane-6-carboxylic acid (2.305). A suspension of compound **2.293** (0.052 g, 0.870 mmol) and 10 % w/w Pd/C (10 mg) in EtOH (0.5 mL) was stirred under an atmosphere of H₂ (gas) at room temperature for 3 h. The mixture was filtered through a short pad of Celite, rinsed with EtOH (5 mL), and the filtrate and washings were concentrated to dryness to give 0.044 g (>99%) of **2.305** as an amorphous solid, which was carried on without further purification: ¹H NMR (CDCl₃, 400 MHz) δ 7.60-7.57 (comp, 4 H), 7.47-7.34 (comp, 11 H), 4.26-4.81 (comp, 2 H), 3.99-3.93 (m, 1 H), 3.73 (s, 3 H), 2.96 (app q, *J* = 3.2 Hz, 1 H), 2.78-2.70 (comp, 2 H), 2.16-2.08 (m, 1 H), 1.83 (d, *J* = 17.6 Hz, 1 H), 1.58-1.52 (m, 1 H), 1.40-1.35 (m, 1 H), 1.04 (s, 9 H); LCMS (ESI) *m/z* 506 [C₂₈H₃₂NO₆Si (M+H) requires 506].

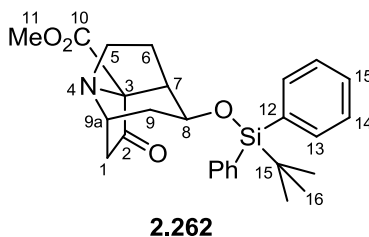
NMR Assignments. ¹H NMR (CDCl₃, 400 MHz) δ 7.60-7.57 (comp, 4 H, Ar-H), 7.47-7.34 (comp, 11 H, Ar-H), 4.26-4.81 (comp, 2 H, C5-H/C8-H), 3.99-3.93 (m, 1 H, C9a-H), 3.73 (s, 3 H, C11-H), 2.96 (app q, *J* = 3.2 Hz, 1 H, C7-H), 2.78-2.70 (comp, 2 H, C6-H), 2.16-2.08 (m, 1 H, C1-Hb), 1.83 (d, *J* = 17.6 Hz, 1 H, C1-Ha), 1.58-1.52 (m, 1 H, C9-H), 1.40-1.35 (m, 1 H, C9-H), 1.04 (s, 9 H, C14-H).



Methyl 3-[(*tert*-butyldiphenylsilyl)oxy]-9-oxo-7-azatricyclo[5.3.0.0^{4,8}]decane-8-carboxylate (2.262). A mixture of acid **2.305** (0.011 g, 0.0217 mmol), disulfide **2.306a** (0.008 g, 0.0303 mmol), and Bu₃SnH (0.032 g, 0.109 mmol) in THF (0.4 mL) was treated with PBu₃ (0.012 g, 0.0586 mmol) and the reaction was stirred in the dark at room temperature for 4 h. The resulting canary yellow solution was irradiated with a tungsten filament light bulb (200 W) at room temperature for 30 min until the solution became colorless. During the irradiation step it is important to maintain the reaction temperature carefully, as any elevation in temperature results in product consumption. The reaction was then concentrated, and the crude residue was dissolved in EtOAc (5 mL), washed with brine (1 x 5 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography to give 0.05 g **2.262** (50%) as a yellow oil: ¹H NMR (CDCl₃, 400 MHz) δ 7.62-7.58 (comp, 4H), 7.46-7.34 (comp, 6H), 3.96-3.91 (m, 1H), 3.75 (s, 3H), 3.55-3.52 (m, 1H), 3.14 (ddd, *J* = 13.4, 11.4, 4.4 Hz, 1H), 3.02 (dt, *J* = 8.4, 6.0 Hz, 1H), 2.97 (dd, *J* = 6.2, 3.6 Hz, 1H), 2.66-2.60 (m, 1H), 2.36 (ddd, *J* = 13.4, 8.8, 4.4 Hz, 1H), 1.84 (d, *J* = 18.0 Hz, 1H), 1.71 (ddd, *J* = 18.2, 11.0, 5.2 Hz, 1H), 1.65-1.57 (comp, 2H), 1.37-1.32 (comp, 2H), 1.05 (s, 9H); LRMS (CI) *m/z* 464 [C₂₇H₃₄NO₄Si (M+H) requires 464].

NMR Assignments. ¹H NMR (CDCl₃, 400 MHz) δ 7.62-7.58 (comp, 4H), 7.46-7.34 (comp, 6H), 3.96-3.91 (m, 1H), 3.75 (s, 3H), 3.55-3.52 (m, 1H), 3.14 (ddd, *J* = 13.4, 11.4, 4.4 Hz, 1H), 3.02 (dt, *J* = 8.4, 6.0 Hz, 1H), 2.97 (dd, *J* = 6.2, 3.6 Hz, 1H), 2.66-2.60

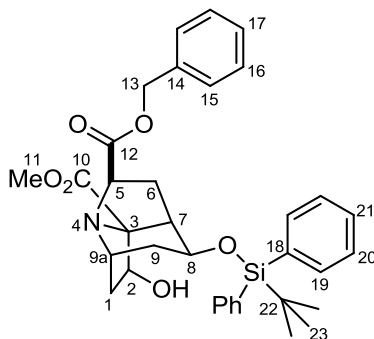
(m, 1H), 2.36 (ddd, $J = 13.4, 8.8, 4.4$ Hz, 1H), 1.84 (d, $J = 18.0$ Hz, 1H), 1.71 (ddd, $J = 18.2, 11.0, 5.2$ Hz, 1H), 1.65-1.57 (comp, 2H), 1.37-1.32 (comp, 2H), 1.05 (s, 9H).



Methyl 3-[(*tert*-butyldiphenylsilyl)oxy]-9-oxo-7-azatricyclo[5.3.0.0^{4,8}]decane-8-carboxylate (2.262). A mixture of acid **2.305** (0.012 g, 0.0236 mmol), pyridine thione **2.306b** (0.004 g, 0.0284 mmol), and DCC (0.004 g, 0.0354 mmol) in CHCl_3 (0.5 mL) was stirred at room temperature for 30 min. The resulting canary yellow solution was irradiated with a tungsten filament light bulb (200 W) at room temperature for 1 h. The reaction was then diluted with CH_2Cl_2 and washed with H_2O (1 x 5 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography eluting with EtOAc to give 0.0065 g (59%) of **2.262** as a colorless oil: ^1H NMR (CDCl_3 , 400 MHz) δ 7.62-7.58 (comp, 4 H), 7.46-7.34 (comp, 6 H), 3.96-3.91 (m, 1 H), 3.75 (s, 3 H), 3.55-3.52 (m, 1 H), 3.14 (ddd, $J = 13.4, 11.4, 4.4$ Hz, 1 H), 3.02 (dt, $J = 8.4, 6.0$ Hz, 1 H), 2.97 (dd, $J = 6.2, 3.6$ Hz, 1 H), 2.66-2.60 (m, 1H), 2.36 (ddd, $J = 13.4, 8.8, 4.4$ Hz, 1 H), 1.84 (d, $J = 18.0$ Hz, 1 H), 1.71 (ddd, $J = 18.2, 11.0, 5.2$ Hz, 1 H), 1.65-1.57 (comp, 2 H), 1.37-1.32 (comp, 2 H), 1.05 (s, 9 H); LRMS (CI) m/z 464 [$\text{C}_{27}\text{H}_{34}\text{NO}_4\text{Si}$ ($\text{M}+\text{H}$) requires 464].

NMR Assignments. ^1H NMR (CDCl_3 , 400 MHz) δ 7.62-7.58 (comp, 4H), 7.46-7.34 (comp, 6H), 3.96-3.91 (m, 1H), 3.75 (s, 3H), 3.55-3.52 (m, 1H), 3.14 (ddd, $J = 13.4, 11.4, 4.4$ Hz, 1H), 3.02 (dt, $J = 8.4, 6.0$ Hz, 1H), 2.97 (dd, $J = 6.2, 3.6$ Hz, 1H), 2.66-2.60

(m, 1H), 2.36 (ddd, $J = 13.4, 8.8, 4.4$ Hz, 1H), 1.84 (d, $J = 18.0$ Hz, 1H), 1.71 (ddd, $J = 18.2, 11.0, 5.2$ Hz, 1H), 1.65-1.57 (comp, 2H), 1.37-1.32 (comp, 2H), 1.05 (s, 9H).

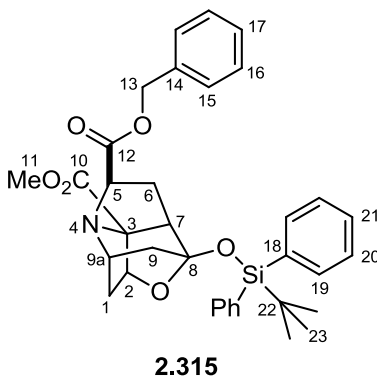


2.313

6-Benzyl-8-methyl-(6*R*)-3-[(*tert*-butyldiphenylsilyl)oxy]-9-hydroxy-7-azatricyclo[5.3.0.0^{4,8}]decane-6,8-dicarboxylate (2.313). A solution of **2.293** (0.085 g, 0.142 mmol) in MeOH (4.7 mL) was cooled to -30 °C and NaBH₄ (0.011 g, 0.284 mmol) was added in one portion. The reaction was stirred at -30 °C for 2 h then warmed slowly to rt over the course of an hour. The reaction was quenched with aq. 1 M HCl (4 mL), and the resulting mixture was concentrated to remove all EtOH. The crude aq. mixture was neutralized with solid K₂CO₃, and then extracted with EtOAc (4 x 10 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated. The crude residue was purified by column chromatography eluting with 4:1 Hex:EtOAc to give 0.063 g (74%) of **2.313** as a colorless oil: ¹H NMR (CDCl₃, 400 MHz) δ 7.67-7.61 (comp, 4H), 7.44-7.31 (comp, 11 H), 5.24 (q, $J = 13.2$ Hz, 2 H), 4.77-4.72 (m, 1 H), 4.37 (dd, $J = 10.4, 3.2$ Hz, 1 H), 4.30 (dd, $J = 11.2, 5.6$ Hz, 1 H), 3.70 (s, 3 H), 3.67-3.62 (m, 1 H), 2.66 (dd, $J = 14.0, 5.6$ Hz, 1 H), 2.51 (dd, $J = 6.0, 3.2$ Hz, 1 H), 2.43-2.35 (m, 1 H), 1.97-1.88 (comp, 2 H), 1.64-1.57 (m, 1 H), 1.43-1.35 (m, 1 H), 1.33-1.09 (comp, 3 H), 1.06 (s, 9 H); ¹³C NMR (CDCl₃, 100 MHz) δ 173.3, 170.9, 135.75, 135.66, 135.6, 134.4,

134.2, 129.5, 129.5, 128.52, 128.48, 128.3, 127.4, 127.4, 80.5, 73.2, 66.7, 65.8, 61.6, 57.0, 52.4, 46.4, 37.4, 35.0, 27.3, 26.9, 19.1; IR (neat) 3233, 2955, 2892, 2857, 1736, 1471, 1225, 1108 cm^{-1} ; HRMS (ESI) m/z 600.2777 [$\text{C}_{35}\text{H}_{42}\text{NO}_6\text{Si}$ (M+H) requires 600.2781].

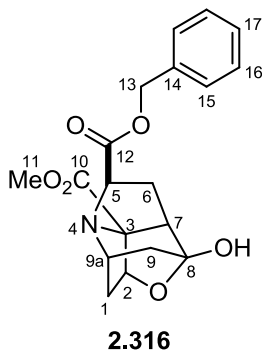
NMR Assignments. ^1H NMR (CDCl_3 , 400 MHz) δ 7.67-7.61 (comp, 4H, Ar-H), 7.44-7.31 (comp, 11 H, Ar-H), 5.24 (q, $J = 13.2$ Hz, 2 H, C13-H), 4.77-4.72 (m, 1 H, C5-H), 4.37 (dd, $J = 10.4, 3.2$ Hz, 1 H, C8-H), 4.30 (dd, $J = 11.2, 5.6$ Hz, 1 H, C9a-H), 3.70 (s, 3 H, C11-H), 3.67-3.62 (m, 1 H, C2-H), 2.66 (dd, $J = 14.0, 5.6$ Hz, 1 H), 2.51 (dd, $J = 6.0, 3.2$ Hz, 1 H), 2.43-2.35 (m, 1 H), 1.97-1.88 (comp, 2 H), 1.64-1.57 (m, 1 H), 1.43-1.35 (m, 1 H), 1.33-1.09 (comp, 3 H), 1.06 (s, 9 H).



4-Benzyl-2-methyl-(4*R*)-7-[(*tert*-butyldiphenylsilyl)oxy]-11-oxa-3-azatetracyclo[5.3.1.0^{2,6}.0^{3,9}]undecane-2,4-dicarboxylate (2.315). A solution of **2.313** (0.032 g, 0.0534 mmol), $\text{PhI}(\text{OAc})_2$ (0.026 g, 0.0800 mmol), and I_2 (0.0136 g, 0.0534 mmol) in CH_2Cl_2 (2.7 mL) was irradiated with tungsten filament light bulb (150 W) at rt for 1.5 h. The reaction was quenched with 10% aq. sodium thiosulfate (3 mL), and extracted with EtOAc (4 x 5 mL). The combined organic layers were dried (MgSO_4), filtered, and concentrated. The crude residue was purified by column chromatography

eluting with Hex:EtOAc (1:1) to give 0.029 g (91 %) of **2.315** as a light yellow oil: ^1H NMR (CDCl_3 , 400 MHz) δ 7.74-7.69 (comp, 4 H), 7.44-7.32 (comp, 11 H), 5.16 (app q, $J = 8.4$ Hz, 2 H), 4.64 (app t, $J = 2.4$ Hz, 1 H), 4.29 (app t, $J = 9.2$ Hz, 1 H), 3.69 (s, 3 H), 3.68-3.64 (m, 1 H), 2.73 (m, 1 H), 2.15-2.10 (comp, 2 H), 1.73-1.66 (comp, 2 H), 1.59 (d, $J = 11.6$ Hz, 1 H), 1.60-1.54 (comp, 2 H), 1.32 (d, $J = 13.6$ Hz, 1 H), 1.27-1.24 (m, 1 H), 1.05 (s, 9 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 171.2, 170.3, 136.0, 135.9, 135.4, 134.3, 134.2, 129.6, 129.6, 128.5, 128.4, 127.33, 127.29, 106.3, 85.0, 79.5, 77.2, 66.7, 63.7, 57.2, 56.9, 52.4, 37.9, 35.7, 29.4, 26.9, 19.1; IR (neat) 2955, 2858, 1736, 1457, 1214 cm^{-1} ; HRMS (ESI) m/z 598.2623 [$\text{C}_{35}\text{H}_{40}\text{NO}_6\text{Si}$ (M+H) requires 598.2625].

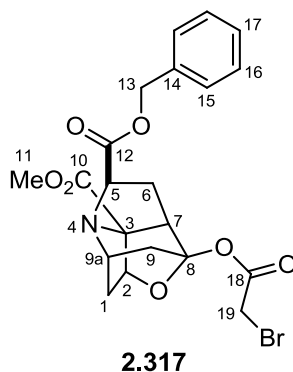
NMR Assignments. ^1H NMR (CDCl_3 , 400 MHz) δ 7.74-7.69 (comp, 4 H, Ar-H), 7.44-7.32 (comp, 11 H, Ar-H), 5.16 (app q, $J = 8.4$ Hz, 2 H, C13-H), 4.64 (app t, $J = 2.4$ Hz, 1 H, C5-H), 4.29 (app t, $J = 9.2$ Hz, 1 H, C9a-H), 3.69 (s, 3 H, C11-H), 3.68-3.64 (m, 1 H, C2-H), 2.73 (m, 1 H), 2.15-2.10 (comp, 2 H), 1.73-1.66 (comp, 2 H), 1.59 (d, $J = 11.6$ Hz, 1 H, C1- H_{endo}), 1.60-1.54 (comp, 2 H), 1.32 (d, $J = 13.6$ Hz, 1 H, C7-H), 1.27-1.24 (m, 1 H), 1.05 (s, 9 H, C16-H).



4-Benzyl-2-methyl-(4*R*)-7-hydroxy-11-oxa-3-azatetracyclo[5.3.1.0^{2,6}.0^{3,9}]undecane-2,4-dicarboxylate (2.316**).** A solution of **2.315** (0.017 g, 0.0284 mmol) and glacial acetic acid (0.003 g, 0.0427 mmol) in THF (0.3 mL) was treated with a solution of

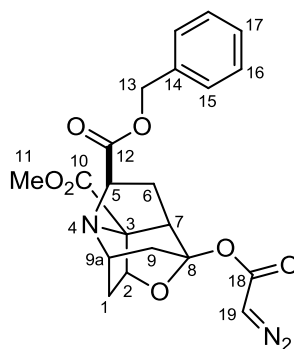
TBAF•3H₂O (0.013 g, 0.0427 mmol), and the resulting solution was stirred at room temperature for 30 min. NEt₃ (0.5 mL) was added to the reaction and the solution was filtered through a short pad of SiO₂, and rinsed with EtOAc:MeOH (10:1 with 1% NEt₃, 30 mL). The filtrate and washings were concentrated to dryness to give 0.095 g (96%) of **2.316** as a colorless oil: ¹H NMR (CDCl₃, 400 MHz) δ 7.74-7.69 (comp, 4 H), 7.44-7.32 (comp, 11 H), 5.16 (app q, *J* = 8.4 Hz, 2 H), 4.64 (app t, *J* = 2.4 Hz, 1 H), 4.29 (app t, *J* = 9.2 Hz, 1 H), 3.69 (s, 3 H), 3.68-3.64 (m, 1 H), 2.73 (m, 1 H), 2.15-2.10 (comp, 2 H), 1.73-1.66 (comp, 2 H), 1.59 (d, *J* = 11.6 Hz, 1 H), 1.60-1.54 (comp, 2 H), 1.32 (d, *J* = 13.6 Hz, 1 H), 1.27-1.24 (m, 1 H), 1.05 (s, 9 H); ¹³C NMR (CDCl₃, 100 MHz, rotamers) δ 171.0, 170.3, 135.3, 128.6, 128.6, 128.5, 105.3, 85.2, 79.6, 67.0, 63.6, 57.3, 55.8, 52.6, 37.9, 34.4, 29.6, 29.4; IR (neat) 3368, 2955, 2850, 1735, 1734, 1455, 1283, 1227, 1134, 1072 cm⁻¹; HRMS (ESI) *m/z* 360.1444 [C₁₉H₂₂NO₆ (M+H) requires 360.1447].

NMR Assignments. ¹H NMR (CDCl₃, 400 MHz) δ 7.74-7.69 (comp, 4 H, Ar-H), 7.44-7.32 (comp, 11 H, Ar-H), 5.16 (app q, *J* = 8.4 Hz, 2 H, C13-H), 4.64 (app t, *J* = 2.4 Hz, 1 H, C5-H), 4.29 (app t, *J* = 9.2 Hz, 1 H, C9a-H), 3.69 (s, 3 H, C11-H), 3.68-3.64 (m, 1 H, C2-H), 2.73 (m, 1 H), 2.15-2.10 (comp, 2 H), 1.73-1.66 (comp, 2 H), 1.59 (d, *J* = 11.6 Hz, 1 H, C1-H_{endo}), 1.60-1.54 (comp, 2 H), 1.32 (d, *J* = 13.6 Hz, 1 H, C7-H), 1.27-1.24 (m, 1 H), 1.05 (s, 9 H, C16-H).



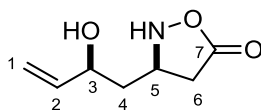
4-Benzyl-2-methyl-7-[(2-bromoacetyl)oxy]-11-oxa-3-azatetracyclo[5.3.1.0^{2,6}.0^{3,9}]undecane-2,4-dicarboxylate (2.317). A solution of **2.316** (0.018 g, 0.0501 mmol), bromoacetic anhydride (0.026 g, 0.100 mmol), NEt₃ (0.010 g, 0.100 mmol), and DMAP (0.001 g, 0.0025 mmol) in CH₂Cl₂ (0.5 mL) was stirred at room temperature for 30 min. The reaction was quenched with saturated aqueous NaHCO₃ (3 mL), and the mixture was extracted with CH₂Cl₂ (3 x 3 mL). The combined organic layers were washed with half saturated NaHCO₃ (3 mL), brine (3 mL). The organic layer was dried (Na₂SO₄), filtered, and concentrated under reduced pressure to provide 0.034 g (>90%) of **2.317** as a crude oil, which was taken on without further purification: ¹H NMR (CDCl₃, 400 MHz) δ 7.39-7.32 (comp, 5 H), 5.23 (app q, *J* = 14.0 Hz, 2 H), 4.93-4.91 (m, 1 H), 4.40 (dd, *J* = 6.8, 10.2 Hz, 1 H), 3.88-3.84 (m, 1 H), 3.79 (s, 2 H), 3.77 (s, 3 H), 3.23 (app d, *J* = 6.4 Hz, 1 H), 2.37-2.32 (comp, 2 H), 2.27-2.22 (m, 1 H), 2.01-1.84 (comp, 3 H).

NMR Assignments. ¹H NMR (CDCl₃, 400 MHz) δ 7.39-7.32 (comp, 5 H, C15-17-H), 5.23 (app q, *J* = 14.0 Hz, 2 H, C13-H), 4.93-4.91 (m, 1 H, C5-H), 4.40 (dd, *J* = 6.8, 10.2 Hz, 1 H), 3.88-3.84 (m, 1 H), 3.79 (s, 2 H, C19-H), 3.77 (s, 3 H, C11-H), 3.23 (app d, *J* = 6.4 Hz, 1 H), 2.37-2.32 (comp, 2 H), 2.27-2.22 (m, 1 H), 2.01-1.84 (comp, 3 H).



2.318

4-Benzyl-2-methyl-7-[(2-diazoacetyl)oxy]-11-oxa-3-azatetracyclo[5.3.1.0^{2,6}.0^{3,9}]undecane-2,4-dicarboxylate (2.318). A solution of crude **2.317** from the previous experimental (0.024 g, 0.0501 mmol) and TsNHNHTs (0.341 g, 0.100 mmol) in THF (1 mL) was cooled to 0 °C, and then DBU (0.038 g, 0.251 mmol) was added dropwise. The reaction was stirred at 0 °C for 30 min, then it was quenched with half saturated NaHCO₃ (1 mL), and the mixture was extracted with Et₂O (3 x 5 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated under reduced pressure to provide a mixture (1:3) of **2.318** and **2.316**.

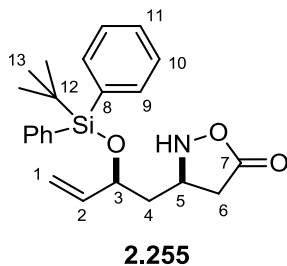


2.254

(3R)-3-[(2S)-2-Hydroxybut-3-en-1-yl]-1,2-oxazolidin-5-one (2.254). A solution of **2.241** (0.080 g, 0.644 mmol), recrystallized hydroxylamine•HCl (0.054 g, 0.773 mmol), and NEt₃ (0.085 g, 0.837 mmol) in EtOH (6.5 mL) was stirred at room temperature for 16 h. The reaction was concentrated under reduced pressure, triturated with Et₂O (10 mL), and the precipitate removed by filtration rinsing with Et₂O (10 mL). The combined filtrate and washings were concentrated under reduced pressure, and the

crude residue was purified by column chromatography eluting with Hex:EtOAc (using a gradient from 1:1 to 3:2) to give 0.049 g (53%) of **2.254** as a light yellow oil: ^1H NMR (CDCl_3 , 400 MHz) δ 5.87 (ddd, $J = 16.8, 10.6, 6.0$ Hz, 1 H), 5.29 (app d, $J = 16.6$ Hz, 1 H), 5.16 (app d, $J = 10.4$ Hz, 1 H), 4.33-4.28 (m, 1 H), 4.09-4.02 (m, 1 H), 2.90 (dd, $J = 7.2, 17$ Hz, 1 H), 2.52 (dd, $J = 6.8, 17.2$ Hz, 1 H), 1.92-1.76 (comp, 2 H), 1.28-1.22 (m, 1 H); LRMS (CI) m/z 158 [$\text{C}_7\text{H}_{12}\text{NO}_3$ (M+H) requires 158].

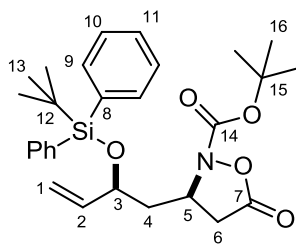
NMR Assignments ^1H NMR (CDCl_3 , 400 MHz) δ 5.87 (ddd, $J = 16.8, 10.6, 6.0$ Hz, 1 H), 5.29 (app d, $J = 16.6$ Hz, 1 H), 5.16 (app d, $J = 10.4$ Hz, 1 H), 4.33-4.28 (m, 1 H), 4.09-4.02 (m, 1 H), 2.90 (dd, $J = 7.2, 17$ Hz, 1 H), 2.52 (dd, $J = 6.8, 17.2$ Hz, 1 H), 1.92-1.76 (comp, 2 H), 1.28-1.22 (m, 1 H).



(3R)-3-[(2S)-2-[(*tert*-Butyldiphenylsilyl)oxy]but-3-en-1-yl]-1,2-oxazolidin-5-one (2.255). A solution of **2.254** (0.052 g, 0.363 mmol), TBDPS-Cl (0.250 g, 0.908 mmol), imidazole (0.074 g, 1.09 mmol), and DMAP (0.004 g, 0.363 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature for 48 h. The reaction was filtered through a pad of Celite rinsing with CH_2Cl_2 (5 mL). The combined filtrate and washings were washed with 0.5 M aqueous HCl (3 x 5 mL). The combined aqueous layers were neutralized with solid K_2CO_3 and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were concentrated under reduced pressure, and the crude residue was purified by column

chromatography eluting with Hex:EtOAc (5:1) to give 0.104 g (72%) of **2.255** as a colorless oil: ^1H NMR (CDCl_3 , 400 MHz) δ 7.68-7.61 (comp, 4 H), 7.47-7.35 (comp, 6 H), 5.81 (ddd, $J = 16.6, 10.4, 5.8$ Hz, 1 H), 5.17-5.06 (comp, 2 H), 4.72-4.65 (m, 1 H), 4.33 (app q, $J = 5.6$ Hz, 1 H), 3.92-3.82 (m, 1 H), 2.54 (dd, $J = 4.8, 17$ Hz, 1 H), 2.30-2.24 (m, 1 H), 1.82-1.73 (m, 1 H), 1.63-1.56 (m, 1 H), 1.08 (s, 9 H); LRMS (CI) m/z 396 [$\text{C}_{23}\text{H}_{30}\text{NO}_3\text{Si}$ ($\text{M}+\text{H}$) requires 396].

NMR Assignments. ^1H NMR (CDCl_3 , 400 MHz) δ 7.68-7.61 (comp, 4 H), 7.47-7.35 (comp, 6 H), 5.81 (ddd, $J = 16.6, 10.4, 5.8$ Hz, 1 H), 5.17-5.06 (comp, 2 H), 4.72-4.65 (m, 1 H), 4.33 (app q, $J = 5.6$ Hz, 1 H), 3.92-3.82 (m, 1 H), 2.54 (dd, $J = 4.8, 17$ Hz, 1 H), 2.30-2.24 (m, 1 H), 1.82-1.73 (m, 1 H), 1.63-1.56 (m, 1 H), 1.08 (s, 9 H).

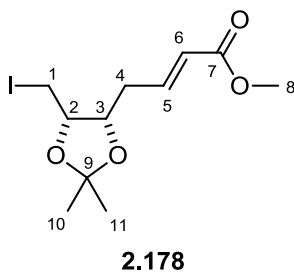


2.256

***tert*-Butyl (3*R*)-3-[(2*S*)-2-[(*tert*-butyldiphenylsilyl)oxy]but-3-en-1-yl]-5-oxo-1,2-oxazolidine-2-carboxylate (**2.255**).** A solution of **2.255** (0.093 g, 0.235 mmol), Boc_2O (0.154 g, 0.705 mmol), NEt_3 (0.071 g, 0.705 mmol), and DMAP (0.003 g, 0.0235 mmol) in CH_2Cl_2 (2.4 mL) was stirred at room temperature for 48 h. The reaction was diluted with CH_2Cl_2 (10 mL) and washed with saturated aqueous NH_4Cl (1 x 10 mL), saturated aqueous NaHCO_3 (2 x 10 mL), and brine (1 x 10 mL). The organic layer was dried (MgSO_4), filtered, and concentrated under reduced pressure. The crude residue was then purified by column chromatography eluting with Hex:EtOAc (6:1) to give 0.093 g

(79%) of **2.256** as a colorless oil: ^1H NMR (CDCl_3 , 400 MHz) δ 7.68-7.61 (comp, 4 H), 7.47-7.34 (comp, 6 H), 5.85 (ddd, $J = 16.8, 10.6, 6.0$ Hz, 1 H), 5.16-5.07 (comp, 2 H), 4.56-4.49 (m, 1 H), 4.34-4.29 (m, 1 H), 2.66 (dd, $J = 8.4, 17.6$ Hz, 1 H), 2.39 (dd, $J = 3.2, 18.0$ Hz, 1 H), 2.12-2.06 (m, 1 H), 1.62-1.55 (m, 1 H), 1.47 (s, 9 H), 1.08 (s, 9 H); LRMS (CI) m/z 496 [$\text{C}_{28}\text{H}_{38}\text{NO}_5\text{Si}$ (M+H) requires 496].

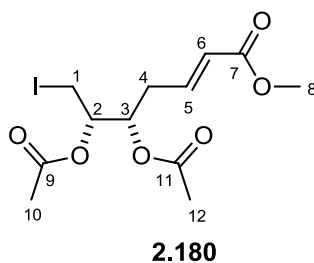
NMR Assignments. ^1H NMR (CDCl_3 , 400 MHz) δ 7.68-7.61 (comp, 4 H), 7.47-7.34 (comp, 6 H), 5.85 (ddd, $J = 16.8, 10.6, 6.0$ Hz, 1 H), 5.16-5.07 (comp, 2 H), 4.56-4.49 (m, 1 H), 4.34-4.29 (m, 1 H), 2.66 (dd, $J = 8.4, 17.6$ Hz, 1 H), 2.39 (dd, $J = 3.2, 18.0$ Hz, 1 H), 2.12-2.06 (m, 1 H), 1.62-1.55 (m, 1 H), 1.47 (s, 9 H), 1.08 (s, 9 H).



(E)-Methyl 4-((4S,5S)-5-(iodomethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoate (2.178). Iodine (0.764 g, 3.01 mmol) was added to a solution of triphenylphosphine (0.781 g, 2.98 mmol) and imidazole (0.270 g, 3.96 mmol) in THF (15 mL) and the reaction was stirred at room temperature for 10 min. A solution of **2.177** (0.457 g, 1.98 mmol) in THF (6.5 mL) was added and the solution was refluxed for 3.5 h until complete consumption of **2.177** was observed by TLC. The reaction was cooled to rt, and poured into a stirred solution of aq. $\text{Na}_2\text{S}_2\text{O}_3$ (5% w/w, 25 mL). EtOAc (25 mL) was added, and the organic layer was removed. The aqueous layer was then extracted with CH_2Cl_2 (2 x 15 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude residue was dissolved in Et_2O (50 mL) and the

precipitate was removed by filtration and rinsed with an additional portion of Et₂O (50 mL). After concentrating the filtrate and washings, the crude residue was purified by flash chromatography eluting with hexanes:Et₂O (4:1) to give 0.490 g (73% yield) of **2.178** as a light yellow oil: ¹H NMR (CDCl₃, 400 MHz) δ 7.03-6.95 (m, 1H), 5.95 (dt, *J* = 15.6, 1.2 Hz, 1H), 4.41 (app q, *J* = 5.2 Hz, 1H), 4.27 (app p, *J* = 4.0 Hz, 1H), 3.73 (s, 3H), 3.23-3.10 (m, 2H), 2.56-2.42 (m, 2H), 1.47 (s, 3H), 1.36 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 166.2, 144.2, 123.2, 108.8, 77.8, 76.0, 51.4, 32.2, 28.2, 28.2, 25.5, 2.3; IR (neat) 2987, 2948, 1721, 1660, 1436, 1381, 1041 cm⁻¹; HRMS (ESI) 363.0080 [C₁₁H₁₇O₄INa (M+Na) requires 363.0064].

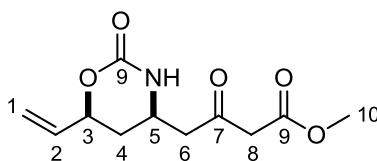
NMR Assignments. ¹H NMR (CDCl₃, 400 MHz) δ 7.03-6.95 (m, 1H, C5-H), 5.95 (dt, *J* = 15.6, 1.2 Hz, 1H, C6-H), 4.41 (app q, *J* = 5.2 Hz, 1H, C2-H), 4.27 (app p, *J* = 4.0 Hz, 1H, C3-H), 3.73 (s, 3H, C8-H), 3.23-3.10 (m, 2H, C1-H), 2.56-2.42 (m, 2H, C4-H), 1.47 (s, 3H, C10-H), 1.36 (s, 3H, C11-H); ¹³C NMR (CDCl₃, 100 MHz) δ 166.2 (C7), 144.2 (C5), 123.2 (C6), 108.8 (C9), 77.8 (C2), 76.0 (C3), 51.4 (C8), 32.2 (C4), 28.2 (C10), 25.5 (C11), 2.3 (C1).



(2S,3S,E)-1-Iodo-7-methoxy-7-oxohept-5-ene-2,3-diyl diacetate (2.180). A suspension of **2.178** (1.38 g, 3.59 mmol) and “activated” Dowex-50 resin (4 g) in anhydrous MeOH (18 mL) was stirred for 24 h at rt. The resin was removed by filtration through a pad of celite, which was rinsed with MeOH (50 mL). The filtrate and washings

were concentrated and a solution of the crude residue, Ac₂O (2 mL), pyridine (4 mL), and DMAP (0.028 g, 0.232 mmol) was stirred at rt for 4 h. EtOAc (20 mL) was added and the solution was washed successively with 1 M HCl (3 x 10 mL), sat. aq. NaHCO₃ (1 x 10 mL), and brine (1 x 10 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated. The resulting crude residue was purified by dissolving in Et₂O (10 mL) and filtering through a short pad of SiO₂ eluting with Et₂O (25 mL) to give 0.857 g (96% yield, 2 steps) of **2.180** as a yellow oil: ¹H NMR (CDCl₃, 400 MHz) δ 6.89-6.81 (m, 1H), 5.88 (dt, *J* = 15.6, 1.2 Hz, 1H), 5.18-5.14 (m, 1H), 5.00-4.96 (m, 1H), 3.73 (s, 3H), 3.36 (dd, *J* = 10.8, 4.0 Hz, 1H), 3.25 (dd, *J* = 11.2, 7.2 Hz, 1H), 2.61-2.47 (m, 2H), 2.12 (s, 3H), 2.07 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 169.5, 169.5, 165.9, 142.4, 123.9, 72.1, 71.5, 51.4, 32.4, 20.6, 20.6, 2.1; IR (neat) 2952, 1746, 1740, 1660, 1436, 1372, 1223, 1040 cm⁻¹; HRMS (ESI) 406.9962 [C₁₂H₁₇O₆INa (M+Na) requires 406.9962].

NMR Assignments. ¹H NMR (CDCl₃, 400 MHz) δ 6.89-6.81 (m, 1H, C5-H), 5.88 (dt, *J* = 15.6, 1.2 Hz, 1H, C6-H), 5.18-5.14 (m, 1H, C2-H), 5.00-4.96 (m, 1H, C3-H), 3.73 (s, 3H, C8-H), 3.36 (dd, *J* = 10.8, 4.0 Hz, 1H, C1-Ha), 3.25 (dd, *J* = 11.2, 7.2 Hz, 1H, C1-Hb), 2.61-2.47 (m, 2H, C4), 2.12 (s, 3H, C10), 2.07 (s, 3H, C12); ¹³C NMR (CDCl₃, 100 MHz) δ 169.5 (C9), 169.5 (C11), 165.9 (C7), 142.4 (C5), 123.9 (C6), 72.1 (C2), 71.5 (C3), 51.4 (C8), 32.4 (C4), 20.6 (C10), 20.6 (C12), 2.1 (C1).

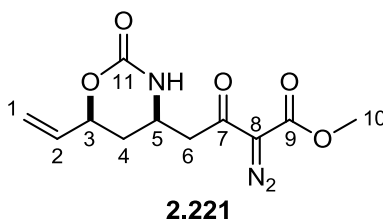


2.219

Methyl 3-oxo-4-((4*R*,6*S*)-2-oxo-6-vinyl-1,3-oxazinan-4-yl)butanoate (2.219).

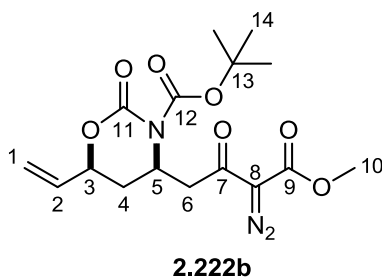
Methyl acetate (0.112 g, 1.51 mmol) was added dropwise to a freshly prepared solution of the LDA (1.51 mmol) in THF (1.5 mL) at -78 °C and the solution was stirred for 1 h. The solution was then transferred by cannula into a flask containing a solution of **2.194** (0.050 g, 0.25 mmol) in THF (0.3 mL) at 0 °C. The resulting solution was stirred at 0 °C for 1 h then warmed to rt and stirred for an additional 1 h. The reaction was quenched with sat. aq. NH₄Cl (5 mL), and EtOAc (5 mL) was added. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (2 x 10 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated. The crude residue was then purified by flash chromatography eluting with EtOAc to give 0.048 g (79%) of **2.219** as a white solid: ¹H NMR (CDCl₃, 400 MHz) δ 6.84 (br s, 1H), 5.91-5.82 (m, 1H), 5.39 (d, *J* = 17.2 Hz, 1H), 5.26 (d, *J* = 10.8 Hz, 1H), 4.75 (q, *J* = 5.2 Hz, 1H), 4.04-3.97 (m, 1H), 3.74 (s, 3H), 3.51 (d, *J* = 4.4 Hz, 2H), 2.85 (d, *J* = 6.4 Hz, 2H), 2.20 (dt, *J* = 14.0, 2.0 Hz, 1H), 1.50 (q, *J* = 13.2 Hz, 1H); LRMS (ESI) 242 [C₁₁H₁₆NO₅ (M+H) requires 242.10].

NMR Assignments. ¹H NMR (CDCl₃, 400 MHz) δ 6.84 (br s, 1H, NH), 5.91-5.82 (m, 1H, C2-H), 5.39 (d, *J* = 17.2 Hz, 1H, C1-H_a), 5.26 (d, *J* = 10.8 Hz, 1H, C1-H_b), 4.75 (q, *J* = 5.2 Hz, 1H, C3-H), 4.04-3.97 (m, 1H, C5-H), 3.74 (s, 3H, C10-H), 3.51 (d, *J* = 4.4 Hz, 2H, C8-H), 2.85 (d, *J* = 6.4 Hz, 2H, C6-H), 2.20 (dt, *J* = 14.0, 2.0 Hz, 1H, C4-H_a), 1.50 (q, *J* = 13.2 Hz, 1H, C4-H_b).



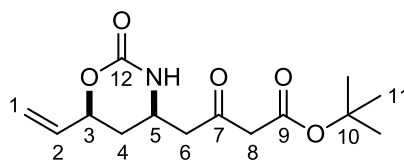
Methyl 2-diazo-3-oxo-4-((4*R*,6*S*)-2-oxo-6-vinyl-1,3-oxazinan-4-yl)butanoate (2.221). NEt₃ (0.185 g, 1.83 mmol) was added dropwise to a solution of **2.219** (0.147 g, 0.609 mmol) and *p*-acetamidobenzenesulfonyl azide (0.220 g, 0.914 mmol) in MeCN:CH₂Cl₂ (1.5 mL, 4:1) and the reaction was stirred at room temperature overnight. Et₂O (5 mL) was then added and the precipitate was removed by filtration and washed with Et₂O (10 mL). The filtrate and washings were concentrated and the crude residue was purified by flash chromatography eluting with EtOAc to give 0.163 g (99 %) of **2.221** as a yellow oil: ¹H NMR (CDCl₃, 400 MHz) δ 6.38 (br s, 1H), 5.92-5.82 (m, 1H), 5.40 (d, *J* = 17.6 Hz, 1H), 5.26 (d, *J* = 10.4 Hz, 1H), 4.76 (q, *J* = 5.2 Hz, 1H), 4.07-4.00 (m, 1H), 3.85 (s, 3H), 3.24 (dd, *J* = 17.6, 4.4 Hz, 1H), 2.95 (dd, *J* = 17.8, 8.4 Hz, 1H), 2.15 (dt, *J* = 14.4, 2.4 Hz, 1H), 1.60 (q, *J* = 11.6 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 189.7, 161.2, 134.8, 117.2, 76.5, 76.4, 52.2, 46.6, 45.6, 33.0; IR (neat) 3263, 2957, 2924, 2140, 1714, 1649, 1650, 1437, 1327 cm⁻¹; HRMS (ESI) 268.0933 [C₁₁H₁₄N₃O₅ (M+H) requires 268.0928].

NMR Assignments. ¹H NMR (CDCl₃, 400 MHz) δ 6.38 (br s, 1H, NH), 5.92-5.82 (m, 1H, C2-H), 5.40 (d, *J* = 17.6 Hz, 1H, C1-H_a), 5.26 (d, *J* = 10.4 Hz, 1H, C1-H_b), 4.76 (q, *J* = 5.2 Hz, 1H, C3-H), 4.07-4.00 (m, 1H, C5-H), 3.85 (s, 3H, C10-H), 3.24 (dd, *J* = 17.6, 4.4 Hz, 1H, C6-H_a), 2.95 (dd, *J* = 17.8, 8.4 Hz, 1H, C6-H_b), 2.15 (dt, *J* = 14.4, 2.4 Hz, 1H, C4-H_a), 1.60 (q, *J* = 11.6 Hz, 1H, C4-H_b); ¹³C NMR (CDCl₃, 100 MHz) δ 189.7 (C7), 161.2 (C9), 134.8 (C11), 117.2 (C1), 76.5 (C3), 76.4 (C8), 52.2 (C5), 46.6 (C4), 45.6 (C6), 33.0 (C10).



(4*R*,6*S*)Methyl-4-(4-*tert*-butoxy-3-diazo-2,4-dioxobutyl)-2-oxo-6-vinyl-1,3-oxazinane-3-carboxylate (2.222b). A solution of **2.221** (0.050 g, 0.162 mmol), NEt₃ (0.049 g, 0.486 mmol), Boc₂O (0.071 g, 0.323 mmol), and DMAP (0.002 g, 0.0162 mmol) in CH₂Cl₂ (0.5 mL) was stirred at room temperature overnight. CH₂Cl₂ (2 mL) was added to the reaction and washed with sat. aq. NaHCO₃ (1 x 3 mL), brine (1 x 3 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated. The crude residue was purified by flash chromatography eluting with hexanes:EtOAc (5:1) to give 0.064 g (97 %) of **2.222b** as a yellow oil: ¹H NMR (CDCl₃, 400 MHz) δ 5.85 (ddd, *J* = 17.6, 11.2, 5.6 Hz, 1H), 5.41 (d, *J* = 17.2 Hz, 1H), 5.28 (d, *J* = 10.8 Hz, 1H), 4.72-4.60 (comp, 2H), 3.84 (s, 3H), 3.40 (dd, *J* = 18.0, 3.6 Hz, 1H), 3.21 (dd, *J* = 18.0, 8.4 Hz, 1H), 2.61 (ddd, *J* = 14.0, 8.8, 2.4 Hz, 1H), 1.73 (ddd, *J* = 15.0, 11.6, 8.8 Hz, 1H), 1.52 (s, 9H); LRMS (ESI) 368 [C₁₆H₂₂N₃O₇ (M+H) requires 368.15].

NMR Assignments. ¹H NMR (CDCl₃, 400 MHz) δ 5.85 (ddd, *J* = 17.6, 11.2, 5.6 Hz, 1H, C2-H), 5.41 (d, *J* = 17.2 Hz, 1H, C1-H_a), 5.28 (d, *J* = 10.8 Hz, 1H, C1-H_b), 4.72-4.60 (comp, 2H, C3-H & C5-H), 3.84 (s, 3H, C10-H), 3.40 (dd, *J* = 18.0, 3.6 Hz, 1H, C6-H_a), 3.21 (dd, *J* = 18.0, 8.4 Hz, 1H, C6-H_b), 2.61 (ddd, *J* = 14.0, 8.8, 2.4 Hz, 1H, C4-H_a), 1.73 (ddd, *J* = 15.0, 11.6, 8.8 Hz, 1H, C4-H_b), 1.52 (s, 9H, C14).



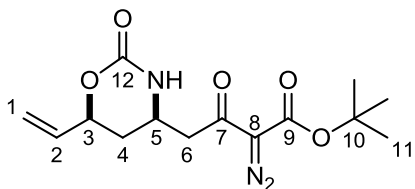
2.218

***tert*-Butyl 3-oxo-4-((4*R*,6*S*)-2-oxo-6-vinyl-1,3-oxazinan-4-yl)butanoate (2.218).**

t-Butyl acetate (0.962 g, 8.28 mmol) was added dropwise to a freshly prepared solution of LDA (8.28 mmol) in THF (8.8 mL) at -78 °C and the solution was stirred for 1 h. The solution was then transferred by cannula into a flask containing a solution of **2.194** (0.275 g, 1.38 mmol) in THF (1.4 mL) at 0 °C. The resulting solution was stirred at 0 °C for 1 h then warmed to rt and stirred for an additional 30 min. The reaction was quenched with sat. aq. NH₄Cl (5 mL), and EtOAc (5 mL) was added. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (2 x 10 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated. The crude residue was then purified by flash chromatography eluting with EtOAc to give 0.391 g (99%) of **2.218** as a colorless oil: ¹H NMR (CDCl₃, 400 MHz) δ 6.84 (br s, 1H), 5.80-5.72 (m, 1H), 5.29 (d, *J* = 16.8 Hz, 1H), 5.14 (d, *J* = 10.8 Hz, 1H), 4.65 (q, *J* = 6.0 Hz, 1H), 3.92-3.85 (m, 1H), 3.29 (d, *J* = 7.2 Hz, 2H), 2.73 (d, *J* = 6.4 Hz, 2H), 2.11 (dt, *J* = 14.0, 2.0 Hz, 1H), 1.42-1.33 (comp, 10H); ¹³C NMR (CDCl₃, 100 MHz) δ 201.0, 165.8, 154.0, 134.7, 117.1, 82.1, 76.7, 50.3, 48.0, 46.0, 32.7, 27.7; LRMS (CI) *m/z* 284 [C₁₄H₂₂NO₅ (M+H) requires 284.15].

NMR Assignments. ¹H NMR (CDCl₃, 400 MHz) δ 6.84 (br s, 1H, NH), 5.80-5.72 (m, 1H, C2-H), 5.29 (d, *J* = 16.8 Hz, 1H, C1-H_a), 5.14 (d, *J* = 10.8 Hz, 1H, C1-H_b), 4.65 (q, *J* = 6.0 Hz, 1H, C3-H), 3.92-3.85 (m, 1H, C5-H), 3.29 (d, *J* = 7.2 Hz, 2H, C8-H), 2.73 (d, *J* = 6.4 Hz, 2H, C6-H), 2.11 (dt, *J* = 14.0, 2.0 Hz, 1H, C4-H_a), 1.42-1.33 (comp, 10H, C11-H & C4-H_b); ¹³C NMR (CDCl₃, 100 MHz) δ 201.0 (C7), 165.8 (C9), 154.0

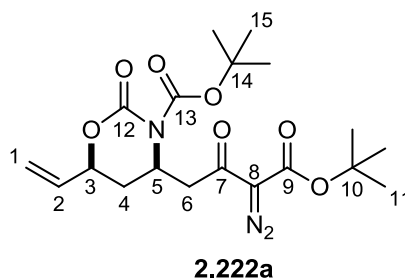
(C12), 134.7 (C2), 117.1 (C1), 82.1 (C3), 76.7 (C10), 50.3 (C8), 48.0 (C6), 46.0 (C5), 32.7 (C4), 27.7 (C11).



2.220

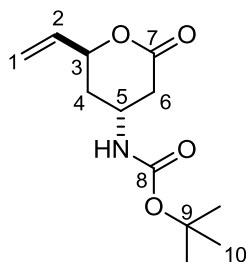
***tert*-Butyl 2-diazo-3-oxo-4-((4*R*,6*S*)-2-oxo-6-vinyl-1,3-oxazinan-4-yl)butanoate (2.220).** NEt₃ (0.107 g, 1.06 mmol) was added dropwise to a solution of **2.220** (0.100 g, 0.353 mmol) and *p*-acetamidobenzenesulfonyl azide (0.127 g, 0.529 mmol) in MeCN (1 mL) and the reaction was stirred at room temperature overnight. Et₂O (5 mL) was then added to the reaction and the precipitate was removed by filtration and washed with Et₂O (10 mL). The filtrate and washings were concentrated and the crude residue was purified by flash chromatography eluting with EtOAc:hexanes (2:1) to give 0.109 g (99 %) of **2.220** as a yellow oil: ¹H NMR (CDCl₃, 400 MHz) δ 6.12 (br s, 1H), 5.85-5.76 (m, 1H), 5.33 (d, *J* = 17.2 Hz, 1H), 5.22 (d, *J* = 10.4 Hz, 1H), 4.72 (q, *J* = 5.2 Hz, 1H), 4.02-3.95 (m, 1H), 3.27 (dd, *J* = 20.0, 3.6 Hz, 1H), 2.81 (dd, *J* = 17.6, 9.2 Hz, 1H), 2.10 (dt, *J* = 14.0, 2.0 Hz, 1H), 1.58 (q, *J* = 14.0 Hz, 1H), 1.48 (s, 9H); LRMS (ESI) 310 [C₁₄H₂₀N₃O₅ (M+1) requires 310].

NMR Assignments. ¹H NMR (CDCl₃, 400 MHz) δ 6.12 (br s, 1H, NH), 5.85-5.76 (m, 1H, C2-H), 5.33 (d, *J* = 17.2 Hz, 1H, C1-H_a), 5.22 (d, *J* = 10.4 Hz, 1H, C1-H_b), 4.72 (q, *J* = 5.2 Hz, 1H, C3-H), 4.02-3.95 (m, 1H, C5-H), 3.27 (dd, *J* = 20.0, 3.6 Hz, 1H, C6-H_a), 2.81 (dd, *J* = 17.6, 9.2 Hz, 1H, C6-H_b), 2.10 (dt, *J* = 14.0, 2.0 Hz, 1H, C4-H_a), 1.58 (q, *J* = 14.0 Hz, 1H, C4-H_b), 1.48 (s, 9H, C11-H).



(4*R*,6*S*)-tert-Butyl 4-(4-tert-butoxy-3-diazo-2,4-dioxobutyl)-2-oxo-6-vinyl-1,3-oxazinane-3-carboxylate (2.222a). A solution of **2.220** (0.050 g, 0.162 mmol), NEt₃ (0.049 g, 0.486 mmol), Boc₂O (0.071 g, 0.323 mmol), and DMAP (0.002 g, 0.0162 mmol) in CH₂Cl₂ (0.5 mL) was stirred at room temperature overnight. CH₂Cl₂ (2 mL) was added to the reaction and washed with sat. aq. NaHCO₃ (1 x 3 mL), brine (1 x 3 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated. The crude residue was purified by flash chromatography eluting with hexanes:EtOAc (5:1) to give 0.064 g (97 %) of **2.222a** as a yellow oil: ¹H NMR (CDCl₃, 400 MHz) δ 5.89-5.81 (m, 1H), 5.40 (d, *J* = 17.6 Hz, 1H), 5.27 (d, *J* = 10.8 Hz, 1H), 4.69-4.60 (comp, 2H), 3.41 (dd, *J* = 18.4, 3.2 Hz, 1H), 3.18 (dd, *J* = 17.6, 8.8 Hz, 1H), 2.68-2.59 (m, 1H), 1.76-1.67 (m, 1H), 1.55-1.48 (comp, 18H). LRMS (ESI) 410 [C₁₉H₂₈N₃O₇ (M+H) requires 410.19].

NMR Assignments. ¹H NMR (CDCl₃, 400 MHz) δ 5.89-5.81 (m, 1H, C2-H), 5.40 (d, *J* = 17.6 Hz, 1H, C1-H_a), 5.27 (d, *J* = 10.8 Hz, 1H, C1-H_b), 4.69-4.60 (comp, 2H, C3-H & C5-H), 3.41 (dd, *J* = 18.4, 3.2 Hz, 1H, C6-H_a), 3.18 (dd, *J* = 17.6, 8.8 Hz, 1H, C6-H_b), 2.68-2.59 (m, 1H, C4-H_a), 1.76-1.67 (m, 1H, C4-H_b), 1.55-1.48 (comp, 18H, C11-H & C15-H).

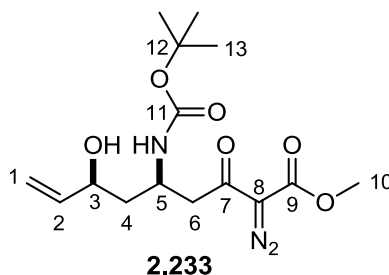


2.230

***tert*-Butyl (4*R*,6*S*)-2-oxo-6-vinyltetrahydro-2*H*-pyran-4-ylcarbamate (2.230).**

A solution of **2.228** (0.150 g, 0.500 mmol) and Cs₂CO₃ (0.02 g, 0.100 mmol) in MeOH (20 mL) was stirred at room temperature for 24 h. The reaction was concentrated and a slurry of the crude residue and SiO₂ (0.150 g) was created and the suspension was concentrated to dryness. The substrate adsorbed silica was dried under high vacuum for 1 h, and then purified by column chromatography eluting with hexanes:EtOAc (2:1) to give 0.103 g (85%) of **2.230** as a colorless oil: ¹H NMR (CDCl₃, 400 MHz) δ 5.93-5.85 (m, 1 H), 5.36 (d, *J* = 17.2 Hz, 1H), 5.29 (d, *J* = 9.6 Hz, 1 H), 5.08-5.03 (m, 1 H), 4.99 (br s, 1 H), 4.09 (br s, 1 H), 2.87 (dd, *J* = 17.6 Hz, 6.8 Hz, 1 H), 2.52 (dd, *J* = 18.0, 6.8 Hz, 1 H), 2.08-1.97 (m, 2 H), 1.47 (s, 9H).

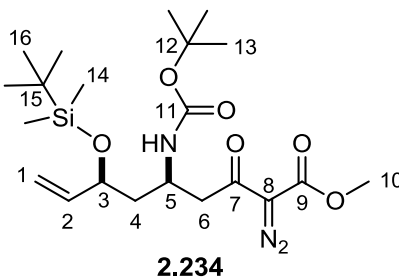
NMR Assignments. ¹H NMR (CDCl₃, 400 MHz) δ 5.93-5.85 (m, 1 H, C2-H), 5.36 (d, *J* = 17.2 Hz, 1 H, C1-H_a), 5.29 (d, *J* = 9.6 Hz, 1 H, C1-H_b), 5.08-5.03 (m, 1 H, C3-H), 4.99 (br s, 1 H, NH), 4.09 (br s, 1 H, C5-H), 2.87 (dd, *J* = 17.6 Hz, 6.8 Hz, 1 H, C6-H_a), 2.52 (dd, *J* = 18.0, 6.8 Hz, 1 H, C6-H_b), 2.08-1.97 (m, 2 H, C4-H), 1.47 (s, 9 H, C10).



(5*R*,7*S*)-Methyl 5-(tert-butoxycarbonylamino)-2-diazo-7-hydroxy-3-oxonon-8-enoate (2.233). A solution of **2.228** (0.388 g, 1.30 mmol) and Cs₂CO₃ (0.052 g, 0.259 mmol) in MeOH (52 mL) was stirred at room temperature for 24 h, and then the reaction was concentrated to dryness. In a separate flask, methyl acetate (0.577 g, 7.80 mmol) was added dropwise to a freshly prepared solution of LDA (7.80 mmol) in THF (7.4 mL) at -78 °C and the solution was stirred for 1 h. The enolate solution was then cannulated into a flask containing a solution of the crude residue from the previous step that had been precooled to 0 °C. The resulting solution was stirred at 0 °C for 1 h then it was warmed to room temperature and stirred for an additional 1 h. The reaction was quenched with saturated aqueous NH₄Cl (40 mL) and diluted with EtOAc (50 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 50 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated, and the crude residue was purified by flash chromatography eluting with Hex:EtOAc (4:1) to give ~0.144 g of **2.226** as crude oil contaminated with ~10% methyl acetoacetate. A solution of crude **2.226**, *p*-acetamidobenzenesulfonyl azide (0.127 g, 0.546 mmol), and NEt₃ (0.254 g, 2.52 mmol) in MeCN (5 mL) was stirred at room temperature overnight. The reaction mixture was concentrated, triturated with Et₂O (20 mL), filtered, and concentrated. The crude residue was purified by column chromatography eluting with Hex:EtOAc (1:1) to give 0.045 g (29%) of **2.233** as a yellow oil: ¹H NMR (CDCl₃, 400 MHz) δ 5.93-5.85 (m, 1H), 5.27 (dt, *J* = 17.2, 1.2 Hz, 1H), 5.12 (dt, *J* = 10.4, 1.2 Hz,

1H), 5.08 (bs, 1H), 4.25-4.22 (m, 1H), 4.21-4.13 (m, 1H), 3.84 (s, 3H), 3.14 (dd, $J = 15.6$, 4.0 Hz, 1H), 3.02 (dd, $J = 15.8$, 6.0 Hz, 1H), 2.61 (bs, 1H), 1.86-1.71 (comp, 2H), 1.42 (s, 3H); LRMS (CI) m/z 342 [$C_{15}H_{24}N_3O_6$ (M+1) requires 342].

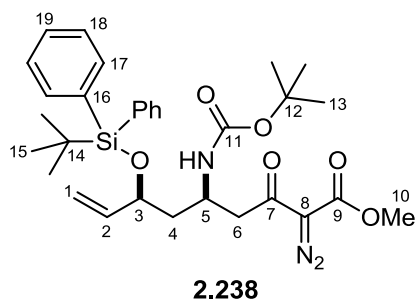
NMR Assignments. 1H NMR ($CDCl_3$, 400 MHz) δ 5.93-5.85 (m, 1H, C2-H), 5.27 (dt, $J = 17.2$, 1.2 Hz, 1H, C1-H), 5.12 (dt, $J = 10.4$, 1.2 Hz, 1H, C1-H), 5.08 (bs, 1H, NH), 4.25-4.22 (m, 1H, C3-H), 4.21-4.13 (m, 1H, C5-H), 3.84 (s, 3H, C10-H), 3.14 (dd, $J = 15.6$, 4.0 Hz, 1H, C6-H), 3.02 (dd, $J = 15.8$, 6.0 Hz, 1H, C6-H), 2.61 (bs, 1H, OH), 1.86-1.71 (comp, 2H, C4-H), 1.42 (s, 3H, C13-H).



(5R,7S)-Methyl 5-(tert-butoxycarbonylamino)-7-(tert-butyldimethylsilyloxy)-2-diazo-3-oxonon-8-enoate (2.234). A solution of **2.233** (0.014 g, 0.041 mmol), TBS-Cl (0.012 g, 0.0821 mmol), and imidazole (0.008 g, 0.123 mmol) in CH_2Cl_2 (0.2 mL) was stirred at rt overnight. The reaction was concentrated and the crude residue purified by column chromatography eluting with Hex:EtOAc (3:1) to give 0.017g (90%) of **2.234** as a yellow oil: 1H NMR ($CDCl_3$, 400 MHz) δ 5.86-5.77 (m, 1H), 5.18 (dt, $J = 17.6$, 1.2 Hz, 1H), 5.13 (bs, 1H), 5.07 (dt, $J = 10.4$, 1.2 Hz, 1H), 4.19 (q, $J = 6.0$ Hz, 1H), 4.07-4.00 (m, 1H), 3.81 (s, 3H), 3.16 (dd, $J = 16.0$, 6.0 Hz, 1H), 2.99 (dd, $J = 16.4$, 4.8 Hz, 1H), 1.84-1.70 (comp, 2H), 1.39 (s, 9H), 0.87 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.1, 161.6, 155.1, 140.5, 114.7, 78.9, 76.4, 72.1, 52.2, 45.4, 45.0,

42.5, 28.3, 25.8, 18.1, -4.4, -5.0; LRMS (CI) m/z 457 [$C_{21}H_{38}N_3O_6Si$ (M+1) requires 457].

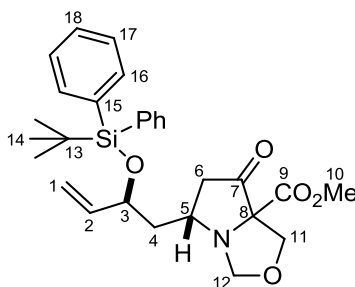
NMR Assignments. 1H NMR ($CDCl_3$, 400 MHz) δ 5.86-5.77 (m, 1 H, C2-H), 5.18 (dt, J = 17.6, 1.2 Hz, 1 H, C1-H), 5.13 (bs, 1 H, NH), 5.07 (dt, J = 10.4, 1.2 Hz, 1 H, C1-H), 4.19 (q, J = 6.0 Hz, 1 H, C3-H), 4.07-4.00 (m, 1 H, C5-H), 3.81 (s, 3 H, C10-H), 3.16 (dd, J = 16.0, 6.0 Hz, 1 H, C6-H), 2.99 (dd, J = 16.4, 4.8 Hz, 1 H, C6-H), 1.84-1.70 (comp, 2 H, C4-H), 1.39 (s, 9 H, C13-H), 0.87 (s, 9 H, C16-H), 0.04 (s, 3 H, C14-H), 0.01 (s, 3 H, C14-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.1 (C7), 161.6 (C9), 155.1 (C11), 140.5 (C2), 114.7 (C1), 78.9 (C12), 76.4 (C3), 72.1 (C8), 52.2 (C10), 45.4 (C4), 45.0, (C6), 42.5 (C5), 28.3 (C13), 25.8 (C16), 18.1 (C15), -4.4 (C14), -5.0 (C14).



Methyl (5*R*,7*S*)-5-[[*tert*-butoxy)carbonyl]amino}-7-[[*tert*-butyldiphenylsilyl)oxy]-2-diazo-3-oxonon-8-enoate (2.238). A solution of **2.233** (0.142 g, 0.416 mmol), TBDPS-Cl (0.229 g, 0.832 mmol), DMAP (0.006 g, 0.0416 mmol), and imidazole (0.085 g, 1.25 mmol) in CH_2Cl_2 (2.0 mL) was stirred at rt for 24 h. The reaction was filtered through Celite and rinsed with CH_2Cl_2 (2 x 5 mL). The filtrate and washings were then washed with 0.5 M aq HCl (1 x 10 mL), and brine (1 x 10 mL), and the organic layer was dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by column chromatography eluting with Hex:EtOAc (4:1) to give 0.190 g

(79%) of **2.238** as a yellow oil: ^1H NMR (CDCl_3 , 400 MHz) δ 7.64-7.60 (comp, 4H), 7.45-7.35 (comp, 6H), 5.86-5.77 (m, 1H), 5.18 (dt, $J = 17.6$, 1.2 Hz, 1H), 5.13 (bs, 1H), 5.07 (dt, $J = 10.4$, 1.2 Hz, 1H), 4.19 (q, $J = 6.0$ Hz, 1H), 4.07-4.00 (m, 1H), 3.81 (s, 3H), 3.16 (dd, $J = 16.0$, 6.0 Hz, 1H), 2.99 (dd, $J = 16.4$, 4.8 Hz, 1H), 1.84-1.70 (comp, 2H), 1.39 (s, 9H), 1.07 (s, 9H); LRMS (CI) m/z 580 [$\text{C}_{31}\text{H}_{42}\text{N}_3\text{O}_6\text{Si}$ (M+H) requires 580].

NMR Assignments. ^1H NMR (CDCl_3 , 400 MHz) δ 7.64-7.60 (comp, 4H, C17-H), 7.45-7.35 (comp, 6H, C18/C19-H), 5.86-5.77 (m, 1H, C2-H), 5.18 (dt, $J = 17.6$, 1.2 Hz, 1H, C1-H), 5.12 (bs, 1H, NH), 5.07 (dt, $J = 10.4$, 1.2 Hz, 1H, C1-H), 4.20 (q, $J = 6.0$ Hz, 1H, C3-H), 4.07-4.00 (m, 1H, C5-H), 3.81 (s, 3H, C10-H), 3.16 (dd, $J = 16.0$, 6.0 Hz, 1H, C6-H), 2.99 (dd, $J = 16.4$, 4.8 Hz, 1H, C6-H), 1.84-1.70 (comp, 2H, C4-H), 1.39 (s, 9H, C13-H), 0.87 (s, 9H, C15-H).

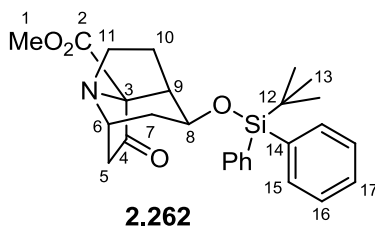


2.240

Methyl (5*R*)-5-[(2*S*)-2-[(*tert*-butyldiphenylsilyl)oxy]but-3-en-1-yl]-7-oxo-hexahydropyrrolo[1,2-*c*][1,3]oxazole-7a-carboxylate (2.240). A mixture of **2.238** (0.190 g, 0.328 mmol) and $\text{Rh}_2(\text{OAc})_4$ (0.007 g, 0.016 mmol) in CH_2Cl_2 (6.6 mL) was stirred at room temperature for 16 h. The reaction mixture was concentrated and the crude residue purified by column chromatography eluting with Hex:EtOAc (5:1) to give 0.181 g (86%) of **2.239** as a mixture (1:1) of diastereomers and rotamers. A solution **2.239** and dimethoxymethane (0.138 g, 1.82 mmol) in TFA: CH_2Cl_2 (1:10, 8.6 mL) was

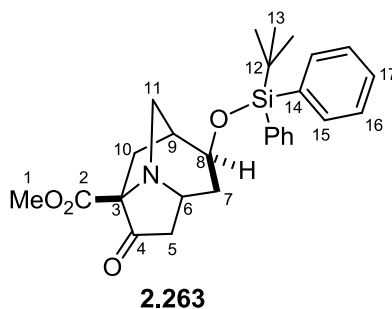
stirred at room temperature for 6 h. The reaction was poured into a separatory funnel, diluted with CH₂Cl₂ (30 mL) and washed with saturate aq. NaHCO₃ (2 x 15 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated and the crude residue was then purified by column chromatography eluting with Hex:EtOAc (using a gradient elution from 1:0 to 6:1) to give 0.017 g (33%) of **2.240** as a mixture (1:1) of diastereomers as a colorless oil : ¹H NMR (CDCl₃, 400 MHz) δ 7.68-7.60 (comp, 4H), 7.47-7.33 (comp, 6H), 5.86-5.78 (m, 1H), 5.05 (dt, *J* = 17.2, 1.2 Hz, 1H), 5.03 (dt, *J* = 10.4, 1.2 Hz, 1H), 4.51 (d, *J* = 7.2 Hz, 1H), 4.23 (dt, *J* = 6.4, 4.8 Hz, 1H), 4.15 (d, *J* = 7.2 Hz, 1H), 4.08 (d, *J* = 9.2 Hz, 1H), 3.92 (d, *J* = 9.2 Hz, 1H), 3.73 (s, 3H), 3.08-3.01 (m, 1H), 2.26 (d, *J* = 7.2 Hz, 1H), 2.25 (d, *J* = 10.0 Hz, 1H), 1.98 (ddd, *J* = 13.8, 6.4, 3.6 Hz, 1H), 1.72 (ddd, *J* = 13.8, 9.4, 4.8 Hz, 1H), 1.07 (s, 9H); LCMS (ESI) *m/z* 494.87 [C₂₈H₃₆NO₅Si (M+H) requires 494.67].

NMR Assignments. ¹H NMR (CDCl₃, 400 MHz) δ 7.68-7.60 (comp, 4H, C16-H), 7.47-7.33 (comp, 6H, C17/C18-H), 5.86-5.78 (m, 1H, C2-H), 5.05 (dt, *J* = 17.2, 1.2 Hz, 1H, C1-H), 5.03 (dt, *J* = 10.4, 1.2 Hz, 1H, C1-H), 4.51 (d, *J* = 7.2 Hz, 1H, C12-H), 4.23 (dt, *J* = 6.4, 4.8 Hz, 1H, C3-H), 4.15 (d, *J* = 7.2 Hz, 1H, C12-H), 4.08 (d, *J* = 9.2 Hz, 1H, C11-H), 3.92 (d, *J* = 9.2 Hz, 1H, C11-H), 3.73 (s, 3H, C10-H), 3.08-3.01 (m, 1H, C5-H), 2.26 (d, *J* = 7.2 Hz, 1H, C4-H), 2.25 (d, *J* = 10.0 Hz, 1H, C4-H), 1.98 (ddd, *J* = 13.8, 6.4, 3.6 Hz, 1H, C6-H), 1.72 (ddd, *J* = 13.8, 9.4, 4.8 Hz, 1H, C6-H), 1.07 (s, 9H, C14-H).



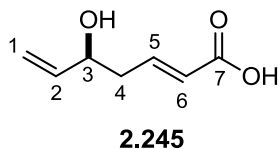
Minor Cycloadduct: Methyl 3-[(*tert*-butyldiphenylsilyl)oxy]-9-oxo-7-azatriscyclo[5.3.0.0^{4,8}]decane-8-carboxylate (2.262**).** A solution of **2.240** (0.019 g, 0.038 mmol) in toluene (3.8 mL) in a sealed tube reaction vessel was heated to 160 °C for 4 h. The reaction was cooled to rt, concentrated, and the crude residue was then purified by column chromatography eluting with Hex:EtOAc (1:1) to give 0.0057 g (32%) of **2.263** as a colorless oil along with 0.011 g (62%) of **2.263** as a colorless oil: ¹H NMR (CDCl₃, 400 MHz) δ 7.62-7.58 (comp, 4H), 7.46-7.34 (comp, 6H), 3.96-3.91 (m, 1H), 3.75 (s, 3H), 3.55-3.52 (m, 1H), 3.14 (ddd, *J* = 13.4, 11.4, 4.4 Hz, 1H), 3.02 (dt, *J* = 8.4, 6.0 Hz, 1H), 2.97 (dd, *J* = 6.2, 3.6 Hz, 1H), 2.66-2.60 (m, 1H), 2.36 (ddd, *J* = 13.4, 8.8, 4.4 Hz, 1H), 1.84 (d, *J* = 18.0 Hz, 1H), 1.71 (ddd, *J* = 18.2, 11.0, 5.2 Hz, 1H), 1.65-1.57 (comp, 2H), 1.37-1.32 (comp, 2H), 1.05 (s, 9H); LRMS (CI) *m/z* 464 [C₂₇H₃₄NO₄Si (M+H) requires 464].

NMR Assignments. ¹H NMR (CDCl₃, 400 MHz) δ 7.62-7.58 (comp, 4H), 7.46-7.34 (comp, 6H), 3.96-3.91 (m, 1H), 3.75 (s, 3H), 3.55-3.52 (m, 1H), 3.14 (ddd, *J* = 13.4, 11.4, 4.4 Hz, 1H), 3.02 (dt, *J* = 8.4, 6.0 Hz, 1H), 2.97 (dd, *J* = 6.2, 3.6 Hz, 1H), 2.66-2.60 (m, 1H), 2.36 (ddd, *J* = 13.4, 8.8, 4.4 Hz, 1H), 1.84 (d, *J* = 18.0 Hz, 1H), 1.71 (ddd, *J* = 18.2, 11.0, 5.2 Hz, 1H), 1.65-1.57 (comp, 2H), 1.37-1.32 (comp, 2H), 1.05 (s, 9H).



Methyl (2*S*,7*S*)-2-[(*tert*-butyldiphenylsilyl)oxy]-6-oxo-8-azatricyclo[5.2.1.0^{4,8}]decane-7-carboxylate (2.263). ¹H NMR (CDCl₃, 400 MHz) δ 7.64-7.60 (comp, 4 H), 7.46-7.35 (comp, 6 H), 3.85-3.79 (comp, 3 H), 3.74 (s, 3 H), 2.81 (dd, J = 15.8, 6.8 Hz, 1 H), 2.63-2.54 (comp, 2 H), 2.28-2.24 (m, 1 H), 2.05 (d, J = 15.6 Hz, 1 H), 1.66-1.60 (m, 1 H), 1.51 (d, J = 14.4 Hz, 1 H), 1.08 (s, 9 H), 0.9 (ddd, J = 15.6, 9.0, 5.2 Hz, 1H); LRMS (CI) m/z 464 [C₂₇H₃₄NO₄Si (M+H) requires 464].

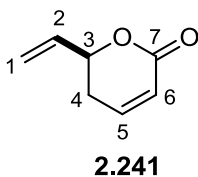
NMR Assignments. ¹H NMR (CDCl₃, 400 MHz) δ 7.64-7.60 (comp, 4H, C15-H), 7.46-7.35 (comp, 6H, C16/C17-H), 3.85-3.79 (comp, 3H, C6/C8-H), 3.74 (s, 3H, C1-H), 2.81 (dd, J = 15.8, 6.8 Hz, 1H, C5-H), 2.63-2.54 (comp, 2H, C11-H), 2.28-2.24 (m, 1H, C9-H), 2.05 (d, J = 15.6 Hz, C5-H), 1.66-1.60 (m, 1H, C10-H), 1.51 (d, J = 14.4 Hz, 1H, C10-H), 1.08 (s, 9H, C13-H), 0.9 (ddd, J = 15.6, 9.0, 5.2 Hz, 1H, C7-H).



(*S*,*E*)-5-Hydroxyhepta-2,6-dienoic acid (2.245). A solution of **2.162** (2.39 g, 15.30 mmol) in 2-propanol:2 M aq. NaOH (46 mL, 2:1) was stirred at rt overnight. The reaction was then concentrated to remove the 2-propanol and the aqueous mixture was washed with CH₂Cl₂ (2 x 20 mL). The aqueous layer was then acidified with 1 M HCl

and extracted with CH₂Cl₂ (4 x 15 mL). The combined org. layers were dried (Na₂SO₄), filtered and concentrated to give 1.75 g (81%) of **2.245** as a light yellow oil requiring no further purification: ¹H NMR (CDCl₃, 400 MHz) δ 7.04 (dt, *J* = 15.6, 7.2 Hz, 1H), 5.92-5.82 (comp, 2H), 5.26 (dt, *J* = 16.8, 1.6 Hz, 1H), 5.15 (dt, *J* = 10.8, 0.8 Hz, 1H), 4.60 (q, *J* = 6.4 Hz, 1H), 2.47 (app t, *J* = 7.2 Hz, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ 171.1, 147.1, 139.4, 123.4, 115.8, 71.5, 39.7; IR (neat) 3382, 3083, 2669, 1697, 1657, 1424, 1257, 982, 929 cm⁻¹; HRMS (CI) *m/z* 143.0705 [C₇H₁₁O₃ (M+H) requires 143.0708].

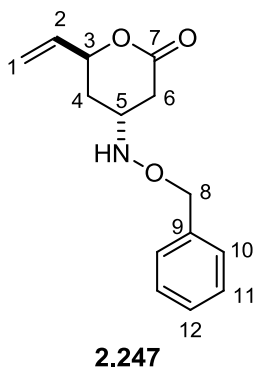
NMR Assignments. ¹H NMR (CDCl₃, 400 MHz) δ 7.04 (dt, *J* = 15.6, 7.2 Hz, 1H, C5-H), 5.92-5.82 (comp, 2H, C6-H & C2-H), 5.26 (dt, *J* = 16.8, 1.6 Hz, 1H, C1-H), 5.15 (dt, *J* = 10.8, 0.8 Hz, 1H, C1-H), 4.60 (q, *J* = 6.4 Hz, 1H, C3-H), 2.47 (app t, *J* = 7.2 Hz, 2H, C4-H); ¹³C NMR (CDCl₃, 100 MHz) δ 171.1 (C7), 147.1 (C5), 139.4 (C2), 123.4 (C6), 115.8 (C1), 71.5 (C3), 39.7 (C4).



(S)-6-Vinyl-5,6-dihydro-2H-pyran-2-one (2.241). A solution of **2.245** (1.75 g, 12.31 mmol) in pyridine (25 mL) was added 2,4,6-trichlorobenzoyl chloride (3.30 g, 13.54 mmol) dropwise over a 30 min period at 0 °C. Reaction was then warmed to room temperature and stirred for 3 h. The reaction mixture was diluted with Et₂O (50 mL) and washed with half saturated aqueous NaHCO₃ (1 x 25 mL), dried (MgSO₄), filtered, and concentrated to remove all excess pyridine. The crude residue was purified by column chromatography eluting with Hex:EtOAc (4:1) to give 1.33 g (87%) of **2.241** as a light yellow oil: ¹H NMR (CDCl₃, 400 MHz) δ 6.95-6.91 (ddd, *J* = 10.0, 5.8, 2.8 Hz, 1 H),

6.03 (ddd, $J = 9.8, 2.4, 1.6$ Hz, 1 H), 6.00-5.92 (m, 1 H), 5.41 (dt, $J = 17.2, 1.2$ Hz, 1 H), 5.30 (dt, $J = 10.4, 1.2$ Hz, 1 H), 4.97-4.92 (m, 1 H), 2.57-2.39 (m, 2 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 163.6, 144.6, 134.6, 121.1, 117.5, 77.6, 29.0; IR (neat) 2916, 1721, 1419, 1385, 1247, 1031 cm^{-1} ; HRMS (CI) m/z 125.0602 [$\text{C}_7\text{H}_9\text{O}_2$ (M+H) requires 125.0603].

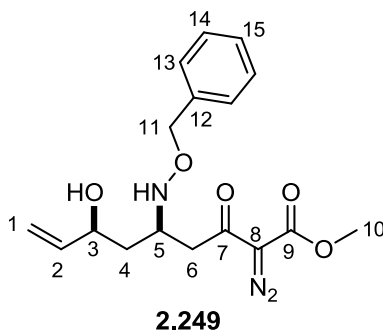
NMR Assignments. ^1H NMR (CDCl_3 , 400 MHz) δ 6.95-6.91 (ddd, $J = 10.0, 5.8, 2.8$ Hz, 1 H, C5-H), 6.03 (ddd, $J = 9.8, 2.4, 1.6$ Hz, 1 H, C6-H), 6.00-5.92 (m, 1 H, C2-H), 5.41 (dt, $J = 17.2, 1.2$ Hz, 1 H, C1-H), 5.30 (dt, $J = 10.4, 1.2$ Hz, 1 H, C1-H), 4.97-4.92 (m, 1 H, C3-H), 2.57-2.39 (m, 2 H, C4-H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 163.6 (C7), 144.6 (C5), 134.6 (C2), 121.1 (C6), 117.5 (C1), 77.6 (C3), 29.0 (C4).



(4R,6S)-4-[(Benzyloxy)amino]-6-ethenyloxan-2-one (2.247). A solution of **2.241** (0.385 g, 3.10 mmol), O-benzylhydroxylamine hydrochloride (0.990 g, 6.20 mmol), and NEt_3 (0.690 g, 6.82 mmol, 0.95 mL) in absolute EtOH (31 mL) was stirred at rt for 48 h. The reaction mixture was concentrated and triturated with Et_2O (30 mL) and the precipitate filtered off. The filtrate was concentrated to dryness to give 0.767 g (99%) of **2.247** as a colorless oil: ^1H NMR (CDCl_3 , 400 MHz) δ 7.38-7.25 (comp, 5H), 5.85-5.76 (m, 1H), 5.45 (bs, 1H), 5.31 (dt, $J = 17.6, 0.8$ Hz, 1H), 5.22 (dt, $J = 10.0, 1.6$ Hz,

1H), 4.97-4.93 (m, 1H), 4.68 (app d, $J = 2.8$, 2H), 3.54 (dt, $J = 10.4$, 5.6 Hz, 1H), 2.68 (dd, $J = 17.2$, 6.0 Hz, 1H), 2.47 (dd, $J = 17.2$, 5.6 Hz, 1H), 1.96 (dt, $J = 10.0$, 4.4 Hz, 1H), 1.80 (ddd, $J = 14.8$, 9.6, 4.8, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 170.2, 137.1, 135.6, 128.6, 128.4, 128.4, 116.9, 77.9, 76.7, 51.0, 33.5, 31.6; LRMS (ESI) m/z 270 [$\text{C}_{14}\text{H}_{17}\text{NO}_3\text{Na}$ ($\text{M}+\text{Na}$) requires 270].

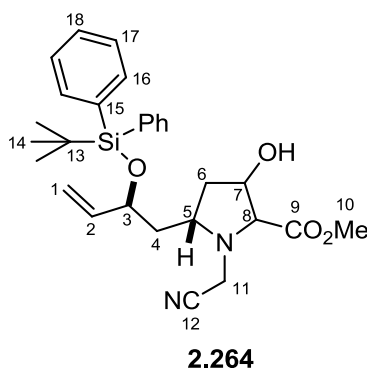
NMR Assignments. ^1H NMR (CDCl_3 , 400 MHz) δ 7.38-7.25 (comp, 5H, C10-H, & C11-H, & C12-H), 5.85-5.76 (m, 1H, C2-H), 5.45 (bs, 1H, NH), 5.31 (dt, $J = 17.6$, 0.8 Hz, 1H, C1-H), 5.22 (dt, $J = 10.0$, 1.6 Hz, 1H, C1-H), 4.97-4.93 (m, 1H, C3-H), 4.68 (app d, $J = 2.8$, 2H, C8-H), 3.54 (dt, $J = 10.4$, 5.6 Hz, 1H, C5-H), 2.68 (dd, $J = 17.2$, 6.0 Hz, 1H, C6-H), 2.47 (dd, $J = 17.2$, 5.6 Hz, 1H, C6-H), 1.96 (dt, $J = 10.0$, 4.4 Hz, 1H, C4-H), 1.80 (ddd, $J = 14.8$, 9.6, 4.8, 1H, C4-H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 170.2 (C7), 137.1 (C9), 135.6 (C2), 128.6 (C10), 128.4 (C11), 128.4 (C12), 116.9 (C1), 77.9 (C3), 76.7 (C8), 51.0 (C5), 33.5 (C4), 31.6 (C6).



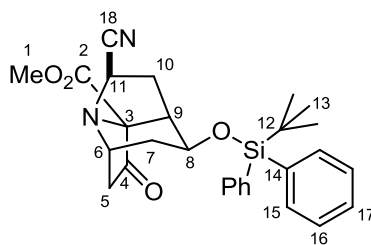
Methyl (5R,7S)-5-[(benzyloxy)amino]-2-diazo-7-hydroxy-3-oxonon-8-enoate (2.249). A solution of methyl acetate (0.689 g, 9.30 mmol, 0.74 mL) in THF (9.3 mL) was added dropwise at a rate of 30 mL/h (using a syringe pump) to a freshly prepared solution of LDA (9.3 mmol) in THF (9.3 mL) at $-78\text{ }^\circ\text{C}$. The reaction was then stirred for 30 min and then a solution of **2.247** (0.767 g, 3.10 mmol) in THF (12 mL) was added

dropwise at a rate of 50 mL/h (using a syringe pump) and the reaction was stirred for an additional 4 h at -78 °C. The reaction was then quenched with 1 M aq. HCl, warmed to rt, and diluted with Et₂O (50mL). The resulting layers were separated and the org. layer was extracted with 1 M aq. HCl (3 x 15 mL). The combined aq. layers were neutralized with solid K₂CO₃ and extracted with CH₂Cl₂ (5 x 10 mL). The combined org. layers were dried (Na₂SO₄), filtered, and concentrated to give the crude crude lactol **2.248** (0.988 g) as a colorless oil requiring no further purification. A solution of the crude residue, *p*-acetamidobenzenesulfonyl azide (0.894 g, 3.72 mmol), and NEt₃ (0.941 g, 9.3 mmol) in MeCN (15.5 mL) was stirred at room temperature for 12 h. The reaction mixture was concentrated and triturated with Et₂O (30 mL) and the precipitate filtered. The filtrate was concentrated and the crude residue was purified by column chromatography eluting with Hex:EtOAc (gradient from 4:1 to 2:1) to give 0.948 g (88%) of **2.249** as a yellow oil: ¹H NMR (CDCl₃, 400 MHz) δ 7.38-7.28 (comp, 5H), 5.86-5.78 (m, 1H), 5.26 (dt, *J* = 17.6, 0.8 Hz, 1H), 5.07 (dt, *J* = 10.0, 1.6 Hz, 1H), 4.71 (dd, *J* = 18.4, 11.6 Hz, 2H), 4.32-4.28 (m, 1H), 3.82 (s, 3H), 3.66-3.60 (m, 1H), 3.35 (dd, *J* = 17.0, 7.2 Hz, 1H), 2.91 (dd, *J* = 17.0, 5.6 Hz, 1H), 1.72-1.55 (comp, 2H); LRMS (ESI) *m/z* 348 [C₁₇H₂₂N₃O₅ (M+Na) requires 348].

NMR Assignments. ¹H NMR (CDCl₃, 400 MHz) δ 7.38-7.28 (comp, 5H, C13-H, C14-H, & C15-H), 5.86-5.78 (m, 1H, C2-H), 5.26 (dt, *J* = 17.6, 0.8 Hz, 1H, C1-H), 5.07 (dt, *J* = 10.0, 1.6 Hz, 1H, C1-H), 4.71 (dd, *J* = 18.4, 11.6 Hz, 2H, C11-H), 4.32-4.28 (m, 1H, C3-H), 3.82 (s, 3H, C10-H), 3.66-3.60 (m, 1H, C5-H), 3.35 (dd, *J* = 17.0, 7.2 Hz, 1H, C6-H), 2.91 (dd, *J* = 17.0, 5.6 Hz, 1H, C6-H), 1.72-1.55 (comp, 2H, C4-H).

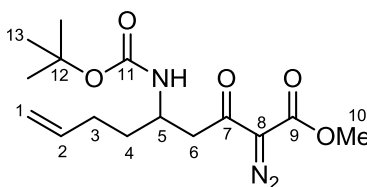


Methyl (5*S*)-5-[(2*S*)-2-[(*tert*-butyldiphenylsilyl)oxy]but-3-en-1-yl]-1-(cyanomethyl)-3-hydroxypyrrolidine-2-carboxylate (2.264). A solution of **2.239** (0.055 g, 0.0997 mmol) and NaBH₄ (0.004 g, 0.0997 mmol) in MeOH (1 mL) was stirred at room temperature for 0.5 h. The reaction was quenched with 0.5 M aq HCl and concentrated to remove all MeOH. The aq. mixture was then extracted with CH₂Cl₂ (3 x 5 mL), and the combined organic layers were dried (Na₂SO₄), filtered, and concentrated. The crude residue was dissolved in CH₂Cl₂ (0.5 mL), cooled to 0 °C, and neat TFA (0.226 g, 1.99 mmol, 150 μL) was added dropwise. The reaction was then warmed to rt and stirred for 2 h. The reaction was concentrated to dryness and pumped down under high vac for 2 h to remove all volatile components. The crude residue was then dissolved in MeCN (1 mL), cooled to 0 °C, and NEt(*i*-Pr)₂ (0.032 g, 0.248 mmol, 43 μL) and iodoacetonitrile (0.017 g, 0.100 mmol, 7 μL) were added sequentially to the reaction. The reaction was warmed to rt and stirred for 12 h. The reaction was then diluted with sat. aq. NaHCO₃ (5 mL) and extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated. The crude residue was then purified by column chromatography eluting with Hex:EtOAc (2:1) to give 0.011 g (22%, 3 steps) of **2.264** as a light yellow oil: *Compound is a mixture of diastereomers, which complicates the NMR. This mixture is inconsequential and is taken on crude.*



2.265

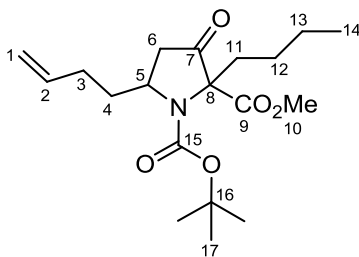
Methyl (6*R*)-3-[(*tert*-butyldiphenylsilyl)oxy]-6-cyano-9-oxo-7-azatricyclo[5.3.0.0^{4,8}]decane-8-carboxylate (2.265). A solution of DMSO (0.015 mL, 0.195 mmol, 14 μ L) in CH₂Cl₂ (0.2 mL) was added dropwise to solution of oxalyl chloride (0.015 g, 0.122 mmol, 11 μ L) in CH₂Cl₂ (1.2 mL) at -78 °C. After 10 min, a solution of **2.264** (0.012 g, 0.0244 mmol) in CH₂Cl₂ (0.25 mL) was added dropwise to the reaction and stirring was continued at -78 °C for 1 h. NEt₃ (0.035 g, 0.342 mmol, 48 μ L) was then added and the reaction was stirred at -78 °C for 16 h. H₂O (1 mL) was then added, the reaction was warmed to room temperature, and the layers separated. The aq. layer was extracted with CH₂Cl₂ (2 x 2 mL), and the combined organic layers were dried (MgSO₄), filtered, and concentrated to give 0.009 g (75%) of **2.265** as a light yellow oil: ¹H NMR (CDCl₃, 400 MHz) δ 7.61-7.57 (m, 4H), 7.47-7.34 (m, 6H), 4.20-4.11 (m, 1H), 3.93-3.90 (m, 1H), 3.75 (s, 3H), 3.00-2.96 (m, 1H), 2.71-2.62 (m, 2H), 2.24-2.16 (m, 1H), 1.96-1.90 (comp, 2H), 1.55-1.43 (comp, 3H), 1.28-1.25 (comp, 2H), 1.06 (s, 9H).



2.85

Methyl 5-[[(*tert*-butoxy)carbonyl]amino]-2-diazo-3-oxonon-8-enoate (2.85). A solution of **2.270** (0.279 g, 0.822 mmol) and **2.271** (0.111 g, 0.781 mmol) in Et₂O (12

mL) was added dropwise to a freshly prepared solution of LiHMDS (1.73 mmol) in Et₂O (4 mL) at -78 °C, and the reaction was stirred at -78 °C for 2 h. The reaction was then quenched with sat. aq. NH₄Cl (10 mL) and the reaction was warmed to rt with vigorous stirring. The resulting layers were separated and the aq. layer was extracted with CH₂Cl₂ (2 x 10 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated. The crude residue was purified by column chromatography eluting with Hex:EtOAc (4:1) to give 0.142 g, (56%) of **2.85** as a bright yellow oil: ¹H NMR (CDCl₃, 400 MHz) spectral data agrees with that previously reported in the group.

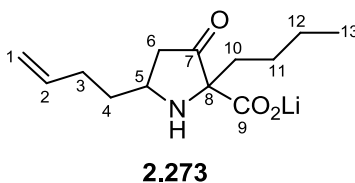


2.272

1-*tert*-Butyl-2-methyl-5-(but-3-en-1-yl)-2-butyl-3-oxopyrrolidine-1,2-dicarboxylate (2.272). A flask containing NaH (0.017 g, 0.706 mmol) was charged with a solution of **2.86** (0.210 g, 0.706 mmol) in DMF (2.0 mL) and the resulting mixture was stirred at rt. Meanwhile a solution of TBAI (0.313 g, 0.847 mmol) and butylbromide (0.145 g, 1.06 mmol, 114 μ L) in DMF (0.5 mL) was prepared and allowed to stir during the course of the deprotonation. After 0.5 h, the butylbromide/TBAI solution was added dropwise to the preformed enolate and the resulting mixture was stirred at rt for 4 h. The reaction was quenched with sat. aq. NH₄Cl (3 mL) and extracted with CH₂Cl₂ (4 x 5 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated. The crude residue was purified by column chromatography eluting with Hex:EtOAc (using a

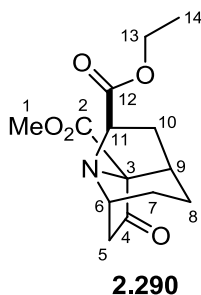
gradient elution from 1:0 to 6:1) to give 0.116 g (46%) of **2.272** as a colorless oil: ^1H NMR (CDCl_3 , 400 MHz, rotamers) δ 5.89-5.79 (m, 1H), 5.08-4.98 (comp, 2H), 4.26-4.14 (m, 1H), 3.73 (s, 3 H), 2.78 (m, 1H), 2.59-2.44 (m, 1H), 2.39-2.27 (m, 1H), 2.17-1.96 (comp, 3H), 1.50 (s, 2 H), 1.43 (s, 7 H), 1.37-1.24 (comp, 2H), 1.21-1.06 (m, 1H), 0.99-0.85 (comp, 4H); LRMS (CI) m/z 354 [$\text{C}_{19}\text{H}_{32}\text{NO}_5$ (M+H) requires 354].

NMR Assignments. : ^1H NMR (CDCl_3 , 400 MHz, rotamers) δ 5.89-5.79 (m, 1H), 5.08-4.98 (comp, 2H), 4.26-4.14 (m, 1H), 3.73 (s, 3H), 2.78 (m, 1H), 2.59-2.44 (m, 1H), 2.39-2.27 (m, 1H), 2.17-1.96 (comp, 3H), 1.50 (s, 2H, minor rotamer/diastereomer), 1.43 (s, 7H, major rotamer/diastereomer), 1.37-1.24 (comp, 2H), 1.21-1.06 (m, 1H), 0.99-0.85 (comp, 4H).



Lithium 5-but-3-enyl-2-butyl 3-oxo-pyrrolidine 2-carboxylate (68). TFA (0.0742 g, 0.651 mmol, 48 μL) was added to a solution of **2.272** (0.023 g, 0.065 mmol) in CH_2Cl_2 (0.2 mL) and the reaction was stirred at rt for 4 h. The reaction was diluted with CH_2Cl_2 (5 mL), washed with sat. aq. NaHCO_3 (1 x 5 mL), dried (Na_2SO_4), filtered, and concentrated. The crude residue was dissolved in THF (0.8 mL) and a 0.33 M solution of LiOH in H_2O (0.004 g, 0.0955 mmol, 8 μL) was added and the reaction was stirred at rt for 12 h. The reaction was concentrated to dryness, dissolved in chloroform, and filtered to give 0.017 g (>99%) of **2.273** as a crude yellow oil which was used without further purification: ^1H NMR (CDCl_3 , 400 MHz) δ 5.87-5.77 (m, 1H), 5.06 (dd, $J = 17.0, 1.6$ Hz, 1H), 5.00 (dd, $J = 10.0, 1.4$ Hz, 1H), 3.38-3.31 (m, 1H), 2.57 (dd, $J = 17.6, 6.0$ Hz,

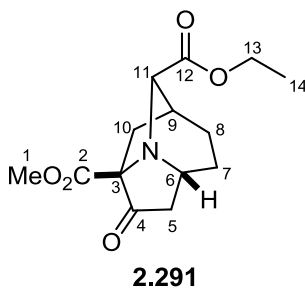
1H), 2.22-2.16 (m, 1H), 2.11 (dd, $J = 17.8, 9.6$ Hz, 1H), 1.96-1.89 (m, 1H), 1.85-1.76 (m, 1H), 1.67-1.58 (m, 1H), 1.35-1.15 (comp, 6H), 0.96-0.87 (comp, 3H).



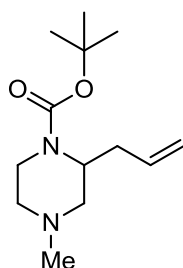
Major Cycloadduct: 6-Ethyl-8-methyl (6*R*)-9-oxo-7-azatricyclo[5.3.0.0^{4,8}]decane-6,8-dicarboxylate (2.290). TFA (0.210 g, 1.84 mmol, 137 μ L) was added dropwise to a solution of **2.85** (0.060 g, 0.184 mmol) in CH_2Cl_2 (0.9 mL) at 0 °C and the reaction was warmed to rt and stirred for 1.5 h. The reaction was then concentrated to dryness and pumped down under high vac for 2 h to remove all volatile components. The crude residue was dissolved in CH_2Cl_2 (0.9 mL) and cooled to 0 °C. NEt_3 (0.019 g, 0.184 mmol, 14 mL) was added dropwise and the reaction was warmed to rt and stirred for 0.5 h. 4Å M.S (0.06 g, in ball form) and ethyl glyoxylate (0.028 g, 0.276 mmol) were then added and the reaction was stirred at rt for 16 h. The reaction was filtered through Celite, rinsed with CH_2Cl_2 (5 mL) and the filtrate concentrated to dryness. The crude residue was dissolved in benzene (3.6 mL) and $\text{Rh}_2(\text{OAc})_4$ (0.004 g, 0.0091 mmol) was added and the mixture was refluxed for 12 h. The reaction was concentrated and the crude residue purified by column chromatography eluting with Hex:EtOAc: NEt_3 (1:1:0.001) to give 0.016 g (34%) of **2.290** as a light yellow oil along with minor cycloadduct **2.291**: ^1H NMR (CDCl_3 , 400 MHz) δ 4.37-4.28 (comp, 2H), 4.26-4.19 (m, 1H), 4.14 (dd, $J = 7.4, 6.0$ Hz, 1H), 3.77 (s, 3H), 3.04-3.00 (m,

1H), 2.94-2.87 (m, 1H), 2.35-2.28 (m, 1H), 2.26 (d, $J = 18.0$ Hz, 1H), 2.21 (dd, $J = 13.2$, 6.4 Hz, 1H), 1.95-1.85 (m, 1H), 1.79-1.68 (m, 1H), 1.56-1.48 (m, 1H), 1.34 (t, $J = 7.2$ Hz, 3H), 1.35-1.25 (m, 1H); LCMS (ESI) m/z 282.2 [$C_{14}H_{20}NO_5$ (M+H) requires 282.13].

NMR Assignments. 1H NMR ($CDCl_3$, 400 MHz) δ 6.89-6.81 (m, 1H, C5-H), 5.88 (dt, $J = 15.6$, 1.2 Hz, 1H, C6-H), 5.18-5.14 (m, 1H, C2-H), 5.00-4.96 (m, 1H, C3-H), 3.73 (s, 3H, C8-H), 3.38-3.23 (m, 2H, C1-H), 2.61-2.47 (m, 2H, C4-H), 2.12 (s, 3H, C10-H), 2.07 (s, 3H, C12-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.50 (C9), 169.45 (C11), 165.9 (C7), 142.4 (C5), 123.9 (C6), 72.1 (C2), 71.5 (C3), 51.4 (C8), 32.4 (C4), 20.63 (C12), 20.61 (C10), 2.1 (C1)



Minor Cycloadduct: 9-Ethyl-7-methyl (4R,7S)-6-oxo-8-azatricyclo[5.2.1.0^{4,8}]decane-7,9-dicarboxylate (2.291). Did not isolate enough of this material to get a good NMR spectrum, however the following signals are indicative of this regioisomeric structure in the NMR spectrum of the reaction mixture: 1H NMR ($CDCl_3$, 400 MHz) δ 2.21 (d, $J = 15.6$ Hz, C5-H), 1.51 (d, $J = 14.4$ Hz, 1H, C10-H).

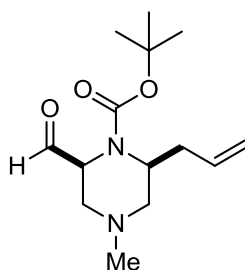


3.122b

***tert*-Butyl 4-methyl-2-(prop-2-en-1-yl)piperazine-1-carboxylate (3.122b).**

Compound **3.118a** (1 g, 4.99 mmol), *s*-BuLi (20 mL of a 0.6 M solution in *n*-hexane, 11.98 mmol), TMEDA (1.39 g, 11.98 mmol), CuCN (1.07 g, 11.98 mmol), LiCl (1.02 g, 23.97 mmol), and allyl bromide (1.45 g, 11.98 mmol) in Et₂O (150 mL) were reacted as reported in literature. Purification *via* flash chromatography eluting with CH₂Cl₂-MeOH (20:1) gave 0.997 g (83%) of **3.122b** as a light yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 5.65-5.77 (m, 1H), 5.03 (d, *J* = 16.8 Hz, 1H), 4.96 (d, *J* = 10.0 Hz, 1H), 4.05 (bs, 1H), 3.81 (d, *J* = 9.6 Hz, 1H), 2.30 (t, *J* = 12.4 Hz, 1H), 2.65 (t, *J* = 10.8 Hz, 2H), 2.34-2.47 (m, 2H), 2.18 (s, 3H), 1.97 (d, *J* = 11.2 Hz, 1H), 1.86 (t, *J* = 12.0 Hz, 1H), 1.40 (s, 9H); ¹³C NMR (CDCl₃, 75 MHz) δ 154.7, 135.3, 116.9, 79.4, 77.2, 57.1, 55.0, 50.7, 46.4, 39.1, 34.6, 28.3; IR (neat) cm⁻¹ 2358, 1698, 1458, 1409, 1365, 1247, 1174, 1106; HRMS (CI) *m/z* 241.1919 [C₁₃H₂₅N₂O₂ (M+H) requires 241.1916].

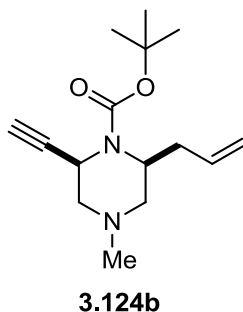
NMR Assignments. ¹H NMR (400 MHz, CDCl₃) δ 5.65-5.77 (m, 1H), 5.03 (d, *J* = 16.8 Hz, 1H), 4.96 (d, *J* = 10.0 Hz, 1H), 4.05 (bs, 1H), 3.81 (d, *J* = 9.6 Hz, 1H), 2.30 (t, *J* = 12.4 Hz, 1H), 2.65 (t, *J* = 10.8 Hz, 2H), 2.34-2.47 (m, 2H), 2.18 (s, 3H), 1.97 (d, *J* = 11.2 Hz, 1H), 1.86 (t, *J* = 12.0 Hz, 1H), 1.40 (s, 9H); ¹³C NMR (CDCl₃, 75 MHz) δ 154.7, 135.3, 116.9, 79.4, 77.2, 57.1, 55.0, 50.7, 46.4, 39.1, 34.6, 28.3.



3.123b

***tert*-Butyl (2,6-*cis*)-2-formyl-4-methyl-6-(prop-2-en-1-yl)piperazine-1-carboxylate (3.123b).** To a mixture of **3.122b** (0.210 g, 0.874 mmol), TMEDA (0.132 g, 1.14 mmol) in Et₂O (20 mL) at -78 °C was added *s*-BuLi (0.95 mL of a 1.2M solution in *n*-hexane, 1.14 mmol). The reaction was warmed to -30 °C and stirred for 1 hr. After cooling reaction back down to -78 °C, DMF (0.96 g, 1.31 mL) was quickly added and reaction was stirred for 1 hr. The reaction was quenched at -78 °C with satd. NH₄Cl, allowed to warm to rt, extracted with Et₂O (4 x 10 mL), and concentrated. The crude oil was then dissolved in hexanes/EtOAc/NEt₃ (98:2:1, 20 mL) and SiO₂ (1.4 g) was added. The reaction was allowed to stir until the disappearance of the *trans*- isomer was observed by TLC (eluting with CH₂Cl₂:MeOH, 20:1). The reaction was filtered, concentrated, and the residue purified *via* flash chromatography eluting with CH₂Cl₂:MeOH (30:1) to give 0.183 g (78%) of **3.123b** as a light yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 9.63 (s, 1H), 5.68-5.79 (m, 1H), 5.98-5.04 (comp, 2H), 4.35 (bs, 1H), 4.00 (bs, 1H), 3.30 (d, *J* = 11.6 Hz, 1H), 2.65 (d, *J* = 10.8 Hz, 1H), 2.21-2.28 (m, 2H), 2.18 (s, 3H), 2.01 (dd, *J* = 6.4, 5.2 Hz, 1H), 1.95 (dd, *J* = 7.6, 4.0 Hz, 1H), 1.48 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 200.4, 154.7, 136.1, 117.1, 79.6, 68.7, 61.2, 54.6, 50.5, 46.5, 39.3, 28.3; ; IR (neat) cm⁻¹ 2968, 2790, 1731, 1690, 1455, 1402, 1367, 1331, 1296, 1173, 1049; HRMS (CI) *m/z* 269.1867 [C₁₄H₂₅N₂O₃ (M+H) requires 269.1865]

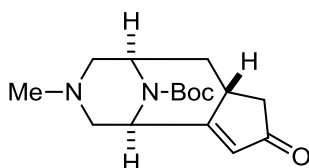
NMR Assignments. ^1H NMR (400 MHz, CDCl_3) δ 9.63 (s, 1H), 5.68-5.79 (m, 1H), 5.98-5.04 (comp, 2H), 4.35 (bs, 1H), 4.00 (bs, 1H), 3.30 (d, $J = 11.6$ Hz, 1H), 2.65 (d, $J = 10.8$ Hz, 1H), 2.21-2.28 (m, 2H), 2.18 (s, 3H), 2.01 (dd, $J = 6.4, 5.2$ Hz, 1H), 1.95 (dd, $J = 7.6, 4.0$ Hz, 1H), 1.48 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 200.4, 154.7, 136.1, 117.1, 79.6, 68.7, 61.2, 54.6, 50.5, 46.5, 39.3, 28.3.



***tert*-Butyl (2,6-*cis*)-2-ethynyl-4-methyl-6-(prop-2-en-1-yl)piperazine-1-carboxylate (3.124b).** To a mixture of **3.123b** (0.480 g, 1.79 mmol), K_2CO_3 (0.742 g, 5.37 mmol) in MeOH (20 mL) at 0 °C was added Bestmann-Ohira reagent (0.688 g, 3.58 mmol). The reaction was warmed to rt and stirred under argon for 16 hr. The reaction was concentrated, dissolved in EtOAc (30 mL), washed with brine H_2O (1 x 10 mL), satd. NaHCO_3 (2 x 10 mL), brine (1 x 10 mL). The organic layer was dried (MgSO_4), filtered, concentrated, and the residue was purified *via* flash chromatography eluting with CH_2Cl_2 :MeOH (30:1) to give 0.379 g (80%) of **3.124b** as a colorless oil: ^1H NMR (400 MHz, CDCl_3) δ 5.74-5.85 (m, 1 H), 5.14 (d, $J = 17.2$, 1 H), 5.05 (d, $J = 10.4$, 1 H), 4.85 (bs, 1 H), 4.00 (m, 1 H), 2.93 (dt, $J = 11.6, 2.0$ Hz, 1 H), 2.72-2.82 (comp, 2 H), 2.60-2.67 (m, 1 H), 2.28 (s, 3 H), 2.22 (d, $J = 2.4$ Hz, 1 H), 2.09 (dd, $J = 7.2, 4.0$ Hz, 1 H), 1.95 (dd, $J = 7.2, 4.0$, 1 H), 1.45 (s, 9 H); ^{13}C NMR (75 MHz, CDCl_3) δ 154.2, 135.1, 117.0, 85.2, 77.5, 67.7, 61.5, 60.4, 50.4, 45.1, 39.4, 39.1, 28.7; IR (neat) cm^{-1} 3295, 2978,

2942, 2802, 1696, 1455, 1390, 1337, 1296, 1249, 1179, 1044; HRMS (CI) m/z 265.1912 [$C_{15}H_{25}N_2O_2$ (M+H) requires 265.1916].

NMR Assignments. 1H NMR (400 MHz, $CDCl_3$) δ 5.74-5.85 (m, 1 H), 5.14 (d, J = 17.2, 1 H), 5.05 (d, J = 10.4, 1 H), 4.85 (bs, 1 H), 4.00 (m, 1 H), 2.93 (dt, J = 11.6, 2.0 Hz, 1 H), 2.72-2.82 (comp, 2 H), 2.60-2.67 (m, 1 H), 2.28 (s, 3 H), 2.22 (d, J = 2.4 Hz, 1 H), 2.09 (dd, J = 7.2, 4.0 Hz, 1 H), 1.95 (dd, J = 7.2, 4.0, 1 H), 1.45 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 135.1, 117.0, 85.2, 77.5, 67.7, 61.5, 60.4, 50.4, 45.1, 39.4, 39.1, 28.7; LRMS (CI) m/z 265 [$C_{15}H_{25}N_2O_2$ (M+1) requires 265.19], 249, 237, 223, 209, 165, 154.154.7, 135.3, 116.9, 79.4, 77.2, 57.1, 55.0, 50.7, 46.4, 39.1, 34.6, 28.3.

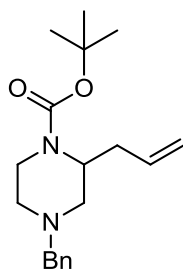


3.125b

***tert*-Butyl 10-methyl-4-oxo-10,12-diazatricyclo[6.3.1.0^{2,6}]dodec-2-ene-12-carboxylate (3.125b).** To a mixture of **3.124b** (0.147 g, 0.556 mmol) in THF (18 mL) was added $Co_2(CO)_8$ (0.289 g, 0.834 mmol) and the resulting mixture was warmed to 40 °C for 1 hr until the consumption of the starting material was observed by TLC (eluting with Hex:EtOAc, 3:1). To the reaction was added DMSO (0.260 g, 3.34 mmol) and the reaction was heated at 50 °C for 16 h. Concentrated reaction mixture and purified *via* flash chromatography eluting with hexanes:EtOAc (2:1) to give 0.137 g (85%) of **3.125b** as a colorless oil: 1H NMR (500 MHz, d_6 -DMSO, 100 °C) δ 5.86 (d, J = 2.1 Hz, 1H), 4.92 (s, 1H), 4.14 (s, 1H), 3.99-4.05 (m, 1H), 2.92 (d, J = 11.2 Hz, 1H), 2.87 (d, J = 11.6 Hz, 1H), 2.48 (dd, J = 18.2, 6.5, 1H), 2.32 (dd, J = 11.5, 3.3 Hz, 1H), 2.26 (dd, J = 1.8, 1.7 Hz, 1H), 2.24 (dd, J = 1.8, 1.7 Hz, 1H), 2.19 (s, 3H), 2.17 (m, 1H), 1.79 (dd, J = 18.2,

3.3 Hz, 1H), 1.87 (m, 1H), 1.40 (s, 9H); ^{13}C NMR (125 MHz, $\text{d}_6\text{-DMSO}$, 100 $^\circ\text{C}$) 206.1, 178.6, 152.5, 127.6, 125.4, 79.0, 57.9, 56.4, 57.9, 56.4, 44.6, 42.6, 38.0, 37.6, 27.5; IR (neat) cm^{-1} 2973, 2920, 2791, 1696, 1623, 1458, 1407, 1322, 1173, 1046; HRMS (CI) m/z 293.1866 [$\text{C}_{16}\text{H}_{25}\text{N}_2\text{O}_3$ (M+1) requires 293.1865].

NMR Assignments. ^1H NMR (500 MHz, $\text{d}_6\text{-DMSO}$, 100 $^\circ\text{C}$) δ 5.86 (d, $J = 2.1$ Hz, 1H), 4.92 (s, 1H), 4.14 (s, 1H), 3.99-4.05 (m, 1H), 2.92 (d, $J = 11.2$ Hz, 1H), 2.87 (d, $J = 11.6$ Hz, 1H), 2.48 (dd, $J = 18.2, 6.5$, 1H), 2.32 (dd, $J = 11.5, 3.3$ Hz, 1H), 2.26 (dd, $J = 1.8, 1.7$ Hz, 1H), 2.24 (dd, $J = 1.8, 1.7$ Hz, 1H), 2.19 (s, 3H), 2.17 (m, 1H), 1.79 (dd, $J = 18.2, 3.3$ Hz, 1H), 1.87 (m, 1H), 1.40 (s, 9H); ^{13}C NMR (125 MHz, $\text{d}_6\text{-DMSO}$, 100 $^\circ\text{C}$) 206.1, 178.6, 152.5, 127.6, 125.4, 79.0, 57.9, 56.4, 57.9, 56.4, 44.6, 42.6, 38.0, 37.6, 27.5.



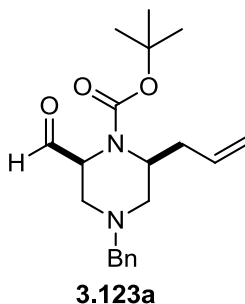
3.122a

***tert*-Butyl 4-benzyl-2-(prop-2-en-1-yl)piperazine-1-carboxylate (3.122a).**

Following the procedure outlined for **3.122b**: Compound **3.118a** (0.20 g, 0.724 mmol), *s*-BuLi (1.19 mL of a 1.46 M solution in *n*-hexane, 1.74 mmol), TMEDA (0.202 g, 1.74 mmol), CuCN (0.156 g, 1.74 mmol), LiCl (0.148 g, 3.48 mmol), and allyl bromide (0.114 g, 0.941 mmol) in Et_2O (25 mL) were allowed to react. Purification via flash chromatography eluting with $\text{CH}_2\text{Cl}_2\text{-MeOH}$ (20:1) yielded 0.193 g (85%) of **3.122a** as a colorless oil: ^1H NMR (400 MHz, CDCl_3) δ 7.22-7.33 (comp, 5H), 5.64-5.74 (m, 1H), 5.00 (d, $J = 16.8$ Hz, 1H), 4.94 (d, $J = 10.0$ Hz, 1H), 4.06 (bs, 1H), 3.84 (d, $J = 9.6$ Hz,

1H), 3.53 (d, $J = 13.2$ Hz, 1H), 3.38 (d, $J = 13.2$ Hz, 1H), 3.07 (td, $J = 12.6, 2.8$ Hz, 1H), 2.76 (d, $J = 10.8$ Hz, 1H), 2.70 (d, $J = 11.2$ Hz, 1H), 2.41-2.53 (m, 1H), 1.99-2.07 (comp, 2H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 154.8, 138.4, 135.5, 128.8, 128.2, 127.0, 117.0, 79.4, 62.8, 54.7, 53.2, 34.6, 28.4; IR (neat) cm^{-1} 3064, 2975, 2807, 1694, 1455, 1410, 1364, 1174; HRMS (CI) m/z 317.2229 [$\text{C}_{19}\text{H}_{29}\text{N}_2\text{O}_2$ (M+1) requires 317.2229].

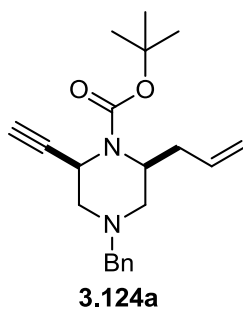
NMR Assignments. ^1H NMR (400 MHz, CDCl_3) δ 7.22-7.33 (comp, 5H), 5.64-5.74 (m, 1H), 5.00 (d, $J = 16.8$ Hz, 1H), 4.94 (d, $J = 10.0$ Hz, 1H), 4.06 (bs, 1H), 3.84 (d, $J = 9.6$ Hz, 1H), 3.53 (d, $J = 13.2$ Hz, 1H), 3.38 (d, $J = 13.2$ Hz, 1H), 3.07 (td, $J = 12.6, 2.8$ Hz, 1H), 2.76 (d, $J = 10.8$ Hz, 1H), 2.70 (d, $J = 11.2$ Hz, 1H), 2.41-2.53 (m, 1H), 1.99-2.07 (comp, 2H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 154.8, 138.4, 135.5, 128.8, 128.2, 127.0, 117.0, 79.4, 62.8, 54.7, 53.2, 34.6, 28.4.



tert-Butyl (2,6-cis)-2-formyl-4-benzyl-6-(prop-2-en-1-yl)piperazine-1-carboxylate (3.123a). Following the procedure outlined for **3.123b**: Compound **3.122a** (0.123 g, 0.389 mmol), TMEDA (0.068 g, 0.584 mmol), Et_2O (13 mL), $s\text{-BuLi}$ (0.4 mL of a 1.46 M solution in $n\text{-hexane}$, 0.584 mmol), and DMF (0.043 g, 0.944 mL) were allowed to react. The crude oil was then dissolved in hexanes/ $\text{EtOAc}/\text{NEt}_3$ (98:2:1, 20 mL) and SiO_2 (0.9 g) was added. The reaction was allowed to stir until the disappearance

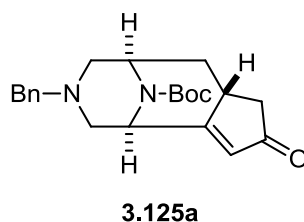
of the trans- isomer was observed by TLC (eluting with CH₂Cl₂:MeOH, 20:1). The reaction was filtered, concentrated, and the residue purified *via* flash chromatography eluting with CH₂Cl₂:MeOH (30:1) to yield 0.109 g (81%) of **3.123a** as a light yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 9.61 (s, 1H), 7.20-7.31 (comp, 5H), 5.59-5.74 (m, 1H), 4.83-5.03 (comp, 2H), 4.46 (bs, 1H), 3.99 (bs, 2H), 3.55 (t, *J* = 16.4 Hz, 1H), 3.35-3.46 (comp, 2H), 2.68-2.77 (m, 1H), 2.41-2.53 (m, 1H), 2.26-3.27 (comp, 2H), 2.21 (dd, *J* = 6.4, 5.2 Hz, 1H), 2.01-2.06 (m, 1H), 1.45-1.48 (rotamers, comp, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 201.9, 154.7, 138.3, 137.6, 135.4, 135.2, 128.7, 128.2, 128.1, 127.2, 117.5, 116.9, 80.6, 79.3, 62.7, 62.4, 53.1, 51.3, 28.2; IR (neat) cm⁻¹ 3072, 2966, 2912, 2801, 2707, 1731, 1690, 1455, 1390, 1367, 1249, 1173; HRMS (CI) *m/z* 345.2179 [C₂₀H₂₉N₂O₃ (M+1) requires 345.2178].

NMR Assignments. ¹H NMR (400 MHz, CDCl₃) δ 9.61 (s, 1H), 7.20-7.31 (comp, 5H), 5.59-5.74 (m, 1H), 4.83-5.03 (comp, 2H), 4.46 (bs, 1H), 3.99 (bs, 2H), 3.55 (t, *J* = 16.4 Hz, 1H), 3.35-3.46 (comp, 2H), 2.68-2.77 (m, 1H), 2.41-2.53 (m, 1H), 2.26-3.27 (comp, 2H), 2.21 (dd, *J* = 6.4, 5.2 Hz, 1H), 2.01-2.06 (m, 1H), 1.45-1.48 (rotamers, comp, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 201.9, 154.7, 138.3, 137.6, 135.4, 135.2, 128.7, 128.2, 128.1, 127.2, 117.5, 116.9, 80.6, 79.3, 62.7, 62.4, 53.1, 51.3, 28.2.



tert-Butyl (2,6-cis)-2-ethynyl-4-benzyl-6-(prop-2-en-1-yl)piperazine-1-carboxylate (3.124a). Following the procedure outlined for **3.124b**: To a mixture of **3.123a** (0.094 g, 0.273 mmol), K₂CO₃ (0.113 g, 0.819 mmol), MeOH (3 mL), Bestmann-Ohira reagent (0.105 g, 0.546 mmol). Purification *via* flash chromatography eluting with CH₂Cl₂:MeOH (30:1) gave 0.071 g (76%) of **3.124a** as a colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 7.20-7.31 (comp, 5H), 5.64-5.74 (m, 1H), 5.01 (d, *J* = 16.1, 1H), 4.95 (d, *J* = 10.0, 1H), 4.07 (bs, 1H), 3.84 (bs, 1H), 3.54 (d, *J* = 13.2 Hz, 1H), 3.38 (d, *J* = 13.2 Hz, 1H), 3.07 (t, *J* = 12.4 Hz, 1H), 2.68-2.79 (comp, 2H), 2.42-2.54 (m, 1H), 2.05 (dd, *J* = 7.6, 4.0 Hz, 1H), 2.00 (d, *J* = 3.6 Hz, 1H), 1.45 (rotamers, comp, 9H): ¹³C NMR (100 MHz, CDCl₃) δ 138.6, 135.7, 129.1, 128.4, 127.3, 117.2, 79.7, 63.1, 54.6, 53.4, 51.6, 28.6; IR (neat) cm⁻¹ 3304, 3074, 2975, 2811, 2773, 1697, 1640, 1454, 1399, 1367, 1336, 1302, 1255, 1175; HRMS (CI) *m/z* 341.2226 [C₂₁H₂₉N₂O₂ (M+1) requires 341.2229].

NMR Assignments. ¹H NMR (400 MHz, CDCl₃) δ 7.20-7.31 (comp, 5H), 5.64-5.74 (m, 1H), 5.01 (d, *J* = 16.1, 1H), 4.95 (d, *J* = 10.0, 1H), 4.07 (bs, 1H), 3.84 (bs, 1H), 3.54 (d, *J* = 13.2 Hz, 1H), 3.38 (d, *J* = 13.2 Hz, 1H), 3.07 (t, *J* = 12.4 Hz, 1H), 2.68-2.79 (comp, 2H), 2.42-2.54 (m, 1H), 2.05 (dd, *J* = 7.6, 4.0 Hz, 1H), 2.00 (d, *J* = 3.6 Hz, 1H), 1.45 (rotamers, comp, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 138.6, 135.7, 129.1, 128.4, 127.3, 117.2, 79.7, 63.1, 54.6, 53.4, 51.6, 28.6.



***tert*-Butyl 10-benzyl-4-oxo-10,12-diazatricyclo[6.3.1.0^{2,6}]dodec-2-ene-12-carboxylate (3.125a).** Following the procedure outlined for **3.125b**: Compound **3.124a** (0.034 g, 0.100 mmol), THF (1 mL), Co₂(CO)₈ (0.098 g, 0.282 mmol), and DMSO (0.088 g, 1.13 mmol) were allowed to react. Purification of the crude residut *via* flash chromatography eluting with hexanes:EtOAc (2:1) provided 0.030 g (81%) of **3.125a** as a colorless oil: ¹H NMR (400MHz, CDCl₃) δ 7.24-7.35 (comp, 5H), 5.93 (s, 1H), 5.86 (s, 1H), 5.07 (s, 1H), 4.90 (s, 1H), 4.20-2.29 (comp, 2H), 3.51 (d, J = 12.8 Hz, 1H), 3.46 (d, J = 12.8 Hz, 1H), 2.89-2.95 (m, 2H), 2.67 (dd, J = 12.0, 6.4 Hz, 1H), 2.50 (dd, J = 8.4, 2.8 Hz, 1H), 2.41 (d, J = 11.2 Hz, 1H), 2.12-2.18 (m, 1H), 1.91 (d, J = 16.0 Hz, 1H), 1.59-1.75 (comp, 2H), 1.43 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) 208.5, 179.6, 179.0, 153.7, 137.5, 128.7, 128.5, 127.3, 126.4, 80.5, 62.9, 56.7, 55.4, 48.9, 47.6, 43.9, 38.7, 28.3; IR (neat) cm⁻¹ 2967, 2920, 2803, 2768, 1692, 1621, 1451, 1315, 1287, 1246, 1175; HRMS (CI) *m/z* 369.2175 [C₂₂H₂₉N₂O₃ (M+1) requires 369.2178].

NMR Assignments. ¹H NMR (400MHz, CDCl₃) δ 7.24-7.35 (comp, 5H), 5.93 (s, 1H), 5.86 (s, 1H), 5.07 (s, 1H), 4.90 (s, 1H), 4.20-2.29 (comp, 2H), 3.51 (d, J = 12.8 Hz, 1H), 3.46 (d, J = 12.8 Hz, 1H), 2.89-2.95 (m, 2H), 2.67 (dd, J = 12.0, 6.4 Hz, 1H), 2.50 (dd, J = 8.4, 2.8 Hz, 1H), 2.41 (d, J = 11.2 Hz, 1H), 2.12-2.18 (m, 1H), 1.91 (d, J = 16.0 Hz, 1H), 1.59-1.75 (comp, 2H), 1.43 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) 208.5, 179.6, 179.0, 153.7, 137.5, 128.7, 128.5, 127.3, 126.4, 80.5, 62.9, 56.7, 55.4, 48.9, 47.6, 43.9, 38.7, 28.3.

REFERENCES

- 1) Coldham, I.; Hufton, R. "Intramolecular Dipolar Cycloaddition Reactions of Azomethine Ylides" *Chem. Rev.* **2005**, *105*, 2765-2809.
- 2) Pearson, W. H.; Clark, R. B. "Formation and Cycloaddition of Nonstabilized N-Unsubstituted Azomethine Ylides from (2-Azaallyl)Stannanes and (2-Azaallyl)Silanes" *Tetrahedron Lett.* **1999**, *40*, 4467-4471.
- 3) Clark, R. B.; Pearson, W. H. "Nonstabilized N-Unsubstituted Azomethine Ylides: A Synthesis of Indolizidine 239cd" *Org. Lett.* **1999**, *1*, 349-351.
- 4) Westling, M.; Smith, R.; Livinghouse, T. "A Convergent Approach to Heterocycle Synthesis Via Silver Ion Mediated A-Ketoimidoyl Halide-Arene Cyclizations. An Application to the Synthesis of the Erythrinane Skeleton" *J. Org. Chem.* **1986**, *51*, 1159-1165.
- 5) Pearson, W. H.; Kropf, J. E.; Choy, A. L.; Lee, I. Y.; Kampf, J. W. "Approach to the Homoerythrina Alkaloids Using a Tandem N-Alkylation/Azomethine Ylide Cycloaddition" *J. Org. Chem.* **2007**, *72*, 4135-4148.
- 6) Smith, R.; Livinghouse, T. "Alkaloid Synthesis Via the Intramolecular Imidate Methylide 1,3-Dipolar Cycloaddition Reaction" *Tetrahedron* **1985**, *41*, 3559-3568.
- 7) Morita, Y.; Tokuyama, H.; Fukuyama, T. "Stereocontrolled Total Synthesis of (-)-Kainic Acid. Regio- and Stereoselective Lithiation of Pyrrolidine Ring with the (+)-Sparteine Surrogate" *Org. Lett.* **2005**, *7*, 4337-4340.
- 8) Hosomi, A.; Sakata, Y.; Sakurai, H. "N-(Trimethylsilylmethyl) Aminomethyl Ethers as Azomethine Ylide Synthons. A New and Convenient Access to Pyrrolidine Derivatives" *Chem. Lett.* **1984**, 1117-1120.
- 9) Padwa, A.; Dent, W. "N-Benzyl-N-Methoxymethyl-N-(Trimethylsilyl) Methylamine as an Azomethine Ylide Equivalent: 2,6-Dioxo-1-Phenyl-4-Benzyl-1,4-Diazobicyclo[3.3.0]Octane" *Org. Synth.* **1993**, 231-235.

- 10) Pandey, G.; Lakshmaiah, G. "Silver(I) Fluoride as One Electron Oxidant for Promoting Sequential Double Desilylation: An Ideal Approach to Non-Stabilized Azomethine Ylides for the Rapid Construction of 1-Azabicyclo(M:3:0)Alkanes" *Tetrahedron Lett.* **1993**, *34*, 4861-4864.
- 11) Pandey, G.; Banerjee, P.; Kumar, R.; Puranik, V. G. "Stereospecific Route to 5,11-Methanomorphanthridine Alkaloids Via Intramolecular 1,3-Dipolar Cycloaddition of Nonstabilized Azomethine Ylide: Formal Total Synthesis of (±)-Pancracine" *Org. Lett.* **2005**, *7*, 3713-3716.
- 12) Pandey, G.; Gupta, N. R.; Pimpalpalle, T. M. "Stereoselective One-Step Construction of Vicinal Quaternary and Tertiary Stereocenters of the 5,10b-Ethanophenanthridine Skeleton: Total Synthesis of (±)-Maritidine" *Org. Lett.* **2009**, *11*, 2547-2550.
- 13) Reissig, H.-U.; Khan, F. A.; Czerwonka, R.; Dinesh, C. U.; Shaikh, A. L.; Zimmer, R. "Benzannulated Cyclooctanol Derivatives by Samarium Diiodide Induced Intramolecular Carbonyl-Alkene Coupling - Scope, Limitations, Stereoselectivity" *Eur. J. Org. Chem.* **2006**, 4419-4428.
- 14) Carra, R. J.; Epperson, M. T.; Gin, D. Y. "Application of an Intramolecular Dipolar Cycloaddition to an Asymmetric Synthesis of the Fully Oxygenated Tricyclic Core of the Stemofoline Alkaloids" *Tetrahedron* **2008**, *64*, 3629-3641.
- 15) Epperson, M. T.; Gin, D. Y. "Enantiospecific Synthesis of the Bridged Pyrrolizidine Core of Asparagamine A: Dipolar Cycloadditions of Azomethine Ylides Derived from the Sulfonylation of Vinylogous Amides" *Angew. Chem., Int. Ed.* **2002**, *41*, 1778-1780.
- 16) Palmisano, G.; Annunziata, R.; Papeo, G.; Sisti, M. "Oxindole Alkaloids. A Novel Non-Biomimetic Entry to (-)-Horsfiline" *Tetrahedron: Asymmetry* **1996**, *7*, 1-4.
- 17) Cravotto, G.; Giovenzana, G. B.; Pilati, T.; Sisti, M.; Palmisano, G. "Azomethine Ylide Cycloaddition/Reductive Heterocyclization Approach to Oxindole Alkaloids: Asymmetric Synthesis of (-)-Horsfiline" *J. Org. Chem.* **2001**, *66*, 8447-8453.

- 18) Bashiardes, G.; Picard, S.; Pornet, J. "Synthesis of Nicotine and Diverse Analogues Using Intramolecular [3+2] Cycloaddition" *Synlett* **2009**, 2497-2499.
- 19) Ma, D.; Xia, C.; Jiang, J.; Zhang, J. "First Total Synthesis of Martinellic Acid, a Naturally Occurring Bradykinin Receptor Antagonist" *Org. Lett.* **2001**, 3, 2189-2191.
- 20) Snider, B. B.; Ahn, Y.; O'Hare, S. M. "Total Synthesis of (±)-Martinellic Acid" *Org. Lett.* **2001**, 3, 4217-4220.
- 21) He, Y.; Mahmud, H.; Moningka, R.; Lovely, C. J.; Dias, H. V. R. "Cyclization Reactions of N-Acryloyl-2-Aminobenzaldehyde Derivatives: Formal Total Synthesis of Martinellic Acid" *Tetrahedron* **2006**, 62, 8755-8769.
- 22) Badarinarayana, V.; Lovely, C. J. "Total Synthesis of (-)-Martinellic Acid" *Tetrahedron Lett.* **2007**, 48, 2607-2610.
- 23) Ueda, M.; Kawai, S.; Hayashi, M.; Naito, T.; Miyata, O. "Efficient Entry into 2-Substituted Tetrahydroquinoline Systems through Alkylative Ring Expansion: Stereoselective Formal Synthesis of (±)-Martinellic Acid" *J. Org. Chem.* **2010**, 75, 914-921.
- 24) Coldham, I.; Jana, S.; Watson, L.; Martin, N. G. "Cascade Condensation, Cyclization, Intermolecular Dipolar Cycloaddition by Multi-Component Coupling and Application to a Synthesis of (±)-Crispine A" *Org. Biomol. Chem.* **2009**, 7, 1674-1679.
- 25) Coldham, I.; Jana, S.; Watson, L.; Pilgram, C. D. "Cascade Cyclization Intermolecular Dipolar Cycloaddition by Multi-Component Couplings-Synthesis of Indolizidines and Pyrrolizidines" *Tetrahedron Lett.* **2008**, 49, 5408-5410.
- 26) Coldham, I.; Burrell, A. J. M.; White, L. E.; Adams, H.; Oram, N. "Highly Efficient Synthesis of Tricyclic Amines by a Cyclization/Cycloaddition Cascade: Total Syntheses of Aspidospermine, Aspidospermidine, and Quebrachamine" *Angew. Chem., Int. Ed.* **2007**, 46, 6159-6162, S6159/6151-S6159/6143.

- 27) Burrell, A. J. M.; Coldham, I.; Watson, L.; Oram, N.; Pilgram, C. D.; Martin, N. G. "Stereoselective Formation of Fused Tricyclic Amines from Acyclic Aldehydes by a Cascade Process Involving Condensation, Cyclization, and Dipolar Cycloaddition" *J. Org. Chem.* **2009**, *74*, 2290-2300.
- 28) Williams, R. M.; Ehrlich, P. P.; Zhai, W.; Hendrix, J. "A New Synthetic Approach to 1-(Hydroxymethyl)-8-Methoxy-1,2,3,4-Tetrahydroisoquinolin-4-One" *J. Org. Chem.* **1987**, *52*, 2615-2617.
- 29) Williams, R. M.; Glinka, T.; Gallegos, R.; Ehrlich, P. P.; Flanagan, M. E.; Coffman, H.; Park, G. "Synthesis, Conformation, Crystal Structures and DNA Cleavage Abilities of Tetracyclic Analogs of Quinocarcin" *Tetrahedron* **1991**, *47*, 2629-2642.
- 30) Flanagan, M. E.; Williams, R. M. "Synthetic Studies on Quinocarcin: Total Synthesis of (±)-Quinocarcinamide Via Dipole Cycloaddition of an Azomethine Ylide Generated by Nbs Oxidation" *J. Org. Chem.* **1995**, *60*, 6791-6797.
- 31) Williams, R. M.; Zhai, W.; Aldous, D. J.; Aldous, S. C. "Asymmetric [1,3]-Dipolar Cycloaddition Reactions: Synthesis of Highly Substituted Proline Derivatives" *J. Org. Chem.* **1992**, *57*, 6527-6532.
- 32) Garner, P.; Ho, W. B.; Shin, H. "The Asymmetric Synthesis of (-)-Quinocarcin Via a 1,3-Dipolar Cycloadditive Strategy" *J. Am. Chem. Soc.* **1993**, *115*, 10742-10753.
- 33) Coldham, I.; Crapnell, K. M.; Fernandez, J.-C.; Moseley, J. D.; Rabot, R. "Synthesis of the Abc Ring System of Manzamine A" *J. Org. Chem.* **2002**, *67*, 6181-6187.
- 34) Ahrendt, K. A.; Williams, R. M. "A Concise Asymmetric Synthesis of the Ade Fragment of Nakadomarin A" *Org. Lett.* **2004**, *6*, 4539-4541.
- 35) Ahrendt, K. A.; Williams, R. M. "A Concise Asymmetric Synthesis of the Ade Fragment of Nakadomarin A. [Erratum to Document Cited in Ca142:094009]" *Org. Lett.* **2005**, *7*, 957.

- 36) Sebahar, P. R.; Williams, R. M. "The Asymmetric Total Synthesis of (+)- and (-)-Spirotryprostatin B" *J. Am. Chem. Soc.* **2000**, *122*, 5666-5667.
- 37) Sebahar, P. R.; Osada, H.; Usui, T.; Williams, R. M. "Asymmetric, Stereocontrolled Total Synthesis of (+) and (-)-Spirotryprostatin B Via a Diastereoselective Azomethine Ylide [1,3]-Dipolar Cycloaddition Reaction" *Tetrahedron* **2002**, *58*, 6311-6322.
- 38) Onishi, T.; Sebahar, P. R.; Williams, R. M. "Concise, Asymmetric Total Synthesis of Spirotryprostatin A" *Tetrahedron* **2004**, *60*, 9503-9515.
- 39) Dietz, J.; Martin, S. F. "Novel Entry to the Tricyclic Core of Stemofoline and Didehydrostemofoline" *Tetrahedron Lett.* **2011**, *52*, 2048-2050.
- 40) Shanahan, C. S.; Fuller, N. O.; Ludolph, B.; Martin, S. F. "Toward a Total Synthesis of the Stemofoline Alkaloids: Advancement of a 1,3-Dipolar Cycloaddition Strategy" *Tetrahedron Letters* **2011**, *In Press, Corrected Proof*,
- 41) Epperson, M. T.; Gin, D. Y. "Enantiospecific Synthesis of the Bridged Pyrrolizidine Core of Asparagamine A: Dipolar Cycloadditions of Azomethine Ylides Derived from the Sulfonylation of Vinylogous Amides" *Angew. Chem., Int. Ed.* **2002**, *41*, 1778-1780.
- 42) Sisko, J.; Weinreb, S. M. "Construction of the Tricyclic Core of the Marine Alkaloid Sarain A" *J. Org. Chem.* **1991**, *56*, 3210-3211.
- 43) Sisko, J.; Henry, J. R.; Weinreb, S. M. "Development of a Strategy for Synthesis of the Unusual Marine Alkaloid Sarain A" *J. Org. Chem.* **1993**, *58*, 4945-4951.
- 44) Griffith, D. A.; Heathcock, C. H. "Progress toward the Synthesis of Sarain A: An Unanticipated Rearrangement" *Tetrahedron Lett.* **1995**, *36*, 2381-2384.
- 45) Heathcock, C. H.; Clasby, M.; Griffith, D. A.; Henke, B. R.; Sharp, M. J. "Progress toward the Synthesis of Sarain A" *Synlett* **1995**, 467-474.

- 46) Denhart, D. J.; Griffith, D. A.; Heathcock, C. H. "Synthesis of the Tricyclic Core of Sarain A. Use of Formaldehyde in an Intramolecular Grigg Azomethine Ylide Cyclization" *J. Org. Chem.* **1998**, *63*, 9616-9617.
- 47) Irie, O.; Samizu, K.; Henry, J. R.; Weinreb, S. M. "Further Studies on Total Synthesis of Sarain A. Efforts toward Annulation of the Macrocyclic Rings" *J. Org. Chem.* **1999**, *64*, 587-595.
- 48) Hong, S.; Yang, J.; Weinreb, S. M. "Construction of an Advanced Tetracyclic Intermediate for Total Synthesis of the Marine Alkaloid Sarain A" *J. Org. Chem.* **2006**, *71*, 2078-2089.
- 49) Blazey, C. M.; Heathcock, C. H. "Regiochemistry in 1,3-Dipolar Cycloadditions of the Azomethine Ylide Formed from Diethyl Aminomalonate and Paraformaldehyde" *J Org Chem* **2002**, *67*, 298-300.
- 50) Kaniskan, H. U.; Garner, P. "An Efficient Synthetic Approach to Cyanocycline a and Bioxalomycin B2 Via [C+Nc+Cc] Coupling" *J. Am. Chem. Soc.* **2007**, *129*, 15460-15461.
- 51) Takano, S.; Imamura, Y.; Ogasawara, K. "Enantioselective Synthesis of Natural Mesembrine Using (D)-Mannitol as a Chiral Template, a Model Study for the Enantioselective Synthesis of the Amaryllidaceae Alkaloids" *Tetrahedron Lett.* **1981**, *22*, 4479-4482.
- 52) Takano, S.; Iwabuchi, Y.; Ogasawara, K. "Concise Enantioselective Synthesis of Acromelic Acid A" *J. Am. Chem. Soc.* **1987**, *109*, 5523-5524.
- 53) Takano, S.; Samizu, K.; Ogasawara, K. "Enantiospecific Construction of Quaternary Carbon Center Via Intramolecular 1,3-Dipolar Cycloaddition. A New Route to Natural (-)-Mesembrine from (S)-O-Benzylglycidol" *Chem. Lett.* **1990**, 1239-1242.
- 54) Hashimura, K.; Tomita, S. i.; Hiroya, K.; Ogasawara, K. "A Stereocontrolled Route to Both Enantiomers of the Necine Base Dihydroxyheliotridane Via Intramolecular 1,3-Dipolar Addition Using the Same Chiral Precursor" *J. Chem. Soc., Chem. Commun.* **1995**, 2291-2292.

- 55) Joucla, M.; Mortier, J. "Flash Vacuum Thermolysis of Oxazolidines: A New Way to Reactive Azomethine Ylides. Regio- and Stereospecific Synthesis of Substituted Pyrrolidines" *Tetrahedron Lett.* **1987**, 28, 2973-2974.
- 56) Joucla, M.; Mortier, J.; Bureau, R. "Flash Vacuum Thermolysis of Oxazolidines: A New Way to Reactive Azomethine Ylides. Ring Closure to Aziridines" *Tetrahedron Lett.* **1987**, 28, 2975-2976.
- 57) Garner, P.; Sunitha, K.; Shanthilal, T. "An Approach to the 3,8-Diazabicyclo[3.2.1]Octane Moiety of Naphthyridinomycin and Quinocarcin Via 1,3-Dipolar Cycloaddition of Photochemically Generated Azomethine Ylides" *Tetrahedron Lett.* **1988**, 29, 3525-3528.
- 58) Garner, P.; Sunitha, K.; Ho, W. B.; Youngs, W. J.; Kennedy, V. O.; Djebli, A. "An Asymmetric Approach to Naphthyridinomycin and Quinocarcin Via a Remarkably Selective Intramolecular 1,3-Dipolar Cycloaddition Reaction" *J. Org. Chem.* **1989**, 54, 2041-2042.
- 59) Garner, P.; Ho, W. B. "Stereoselective 1,3-Dipolar Cycloadditions of Photochemically Generated Azomethine Ylides to Oppolzer's Chiral Acryloyl Sultam. An Asymmetric Approach to Quinocarcin" *J. Org. Chem.* **1990**, 55, 3973-3975.
- 60) Garner, P.; Ho, W. B.; Grandhee, S. K.; Youngs, W. J.; Kennedy, V. O. "Development of an Asymmetric Approach to the 3,8-Diazabicyclo[3.2.1]Octane Moiety of Quinocarcin Via Intramolecular 1,3-Dipolar Cycloadditions of Photochemically Generated Azomethine Ylides" *J. Org. Chem.* **1991**, 56, 5893-5903.
- 61) Garner, P.; Ho, W. B.; Shin, H. "Asymmetric Synthesis of (-)-Quinocarcin" *J. Am. Chem. Soc.* **1992**, 114, 2767-2768.
- 62) Ashley, E. R.; Cruz, E. G.; Stoltz, B. M. "The Total Synthesis of (-)-Lemonomycin" *J. Am. Chem. Soc.* **2003**, 125, 15000-15001.
- 63) Allan, K. M.; Stoltz, B. M. "A Concise Total Synthesis of (-)-Quinocarcin Via Aryne Annulation" *J. Am. Chem. Soc.* **2008**, 130, 17270-17271.

- 64) Peese, K. M.; Gin, D. Y. "Efficient Synthetic Access to the Hetisine C20-Diterpenoid Alkaloids. A Concise Synthesis of Nominine Via Oxidoisoquinolinium-1,3-Dipolar and Dienamine-Diels-Alder Cycloadditions" *J. Am. Chem. Soc.* **2006**, *128*, 8734-8735.
- 65) Peese, K. M.; Gin, D. Y. "Asymmetric Synthetic Access to the Hetisine Alkaloids: Total Synthesis of (+)-Nominine" *Chem.--Eur. J.* **2008**, *14*, 1654-1665.
- 66) Pilli, R. A.; Ferreira de Oliveira, M. C. "Recent Progress in the Chemistry of the Stemona Alkaloids" *Nat. Prod. Rep.* **2000**, *17*, 117-127.
- 67) Jiwajinda, S.; Hirai, N.; Watanabe, K.; Santisopasri, V.; Chuengsamarnyart, N.; Koshimizu, K.; Ohigashi, H. "Occurrence of the Insecticidal 16,17-Didehydro-16(E)-Stemofoline in *Stemona Collinsae*" *Phytochemistry* **2001**, *56*, 693-695.
- 68) Lind, R. J.; Greenhow, D. T.; Blythe, J.; Goodchild, J.; Hirst, E.; Dunbar, S. J.; Earley, F. G. P. "Cyanotropanes: Novel Chemistry Interacting at the Insect Nicotinic Acetylcholine Receptor" *BCPC Conferences - Pets & Diseases* **2002**, *12*, 145-152.
- 69) Sekine, T.; Fukasawa, N.; Kashiwagi, Y.; Ruangrunsi, N.; Murakoshi, I. "Structure of Asparagamine a, a Novel Polycyclic Alkaloid from *Asparagus Racemosus*" *Chem. Pharm. Bull.* **1994**, *42*, 1360-1362.
- 70) Sekine, T.; Ikegami, F.; Fukasawa, N.; Kashiwagi, Y.; Aizawa, T.; Fujii, Y.; Ruangrunsi, N.; Murakoshi, I. "Structure and Relative Stereochemistry of a New Polycyclic Alkaloid, Asparagamine a, Showing Anti-Oxytocin Activity, Isolated from *Asparagus Racemosus*" *J. Chem. Soc., Perkin Trans. 1* **1995**, 391-393.
- 71) Tip-Pyang, S.; Tangpraputgul, P.; Wiboonpun, N.; Veerachato, G.; Phuwapraisirisan, P.; Sup-Udompol, B. "Asparagamine a, an in Vivo Anti-Oxytocin and Antitumor Alkaloid from *Asparagus Racemosus*" *ACGC Chem. Res. Commun.* **2000**, *12*, 31-35.

- 72) Irie, H.; Masaki, N.; Ohno, K.; Osaki, K.; Taga, T.; Uyeo, S. "Crystal Structure of a New Alkaloid, Stemofoline, from *Stemona Japonica*" *J. Chem. Soc. D; Chem. Commun.* **1970**, 1066.
- 73) Kende, A. S.; Smalley, T. L., Jr.; Huang, H. "Total Synthesis of (±)-Isostemofoline" *J. Am. Chem. Soc.* **1999**, *121*, 7431-7432.
- 74) Brueggemann, M.; McDonald, A. I.; Overman, L. E.; Rosen, M. D.; Schwink, L.; Scott, J. P. "Total Synthesis of (±)-Didehydrostemofoline (Asparagamine a) and (±)-Isodidehydrostemofoline" *J. Am. Chem. Soc.* **2003**, *125*, 15284-15285.
- 75) Beddoes, R. L.; Davies, M. P. H.; Thomas, E. J. "Synthesis of the Tricyclic Nucleus of the Alkaloid Stemofoline: X-Ray Crystal Structure of (4rs,5rs,7sr,10rs)-10-Butyl-5-Hydroxy-1-Azatricyclo[5.3.0.0^{4,10}]Decan-2-One" *J. Chem. Soc., Chem. Commun.* **1992**, 538-540.
- 76) Baylis, A. M.; Davies, M. P. H.; Thomas, E. J. "Synthetic Approaches to the Polycyclic Alkaloid Stemofoline" *Org. Biomol. Chem.* **2007**, *5*, 3139-3155.
- 77) Thomas, E. J.; Vickers, C. F. "An Approach to an Asymmetric Synthesis of Stemofoline" *Tetrahedron: Asymmetry* **2009**, *20*, 970-979.
- 78) Davies, H. M. L.; Ahmed, G.; Churchill, M. R. "Asymmetric Synthesis of Highly Functionalized 8-Oxabicyclo[3.2.1]Octene Derivatives" *Journal of the American Chemical Society* **1996**, *118*, 10774-10782.
- 79) Harcken, C. [3+2] Cycloaddition Chemistry - Towards a Total Synthesis of Didehydrostemofoline (Asparagamine a). Dissertation, University of Texas at Austin, Austin, 2002.
- 80) Dietz, J. Progress toward the Total Synthesis of Didehydrostemofoline (Asparagamine a), Stemofoline, and Their Double Bond Stereoisomers Isodidehydrostemofoline and Isostemofoline". Dissertation, University of Texas at Austin, Austin, 2004.

- 81) Ludolph, B. Towards a Total Synthesis of Didehydrostemofoline (Asparagine a) and Stemofoline. Dissertation, University of Texas at Austin, Austin, 2005.
- 82) Fuller, N. O. Progress toward the Total Synthesis of Didehydrostemofoline (Asparagine a) and Related Alkaloids. Dissertation, University of Texas at Austin, Austin, 2007.
- 83) Martin, S. F.; Barr, K. J. "Vinylogous Mannich Reactions. The Asymmetric Total Synthesis of (+)-Croomine" *J. Am. Chem. Soc.* **1996**, *118*, 3299-3300.
- 84) Martin, S. F.; Barr, K. J.; Smith, D. W.; Bur, S. K. "Applications of Vinylogous Mannich Reactions. Concise Enantiospecific Total Syntheses of (+)-Croomine" *J. Am. Chem. Soc.* **1999**, *121*, 6990-6997.
- 85) Concepcion, J. I.; Francisco, C. G.; Hernandez, R.; Salazar, J. A.; Suarez, E. "Intramolecular Hydrogen Abstraction. Iodosobenzene Diacetate, an Efficient and Convenient Reagent for Alkoxy Radical Generation" *Tetrahedron Lett.* **1984**, *25*, 1953-1956.
- 86) Boto, A.; Betancor, C.; Suarez, E. "Hypervalent Iodine Reagents: Synthesis of a Steroidal Orthoacetate by a Radical Reaction" *Tetrahedron Lett.* **1994**, *35*, 6933-6936.
- 87) Francisco, C. G.; Freire, R.; Herrera, A. J.; Perez-Martin, I.; Suarez, E. "Intramolecular 1,5- Versus 1,6-Hydrogen Abstraction Reaction Promoted by Alkoxy Radicals in Carbohydrate Models" *Org. Lett.* **2002**, *4*, 1959-1961.
- 88) Barton, D. H. R.; Beaton, J. M.; Geller, L. E.; Pechet, M. M. "A New Photochemical Reaction" *J. Am. Chem. Soc.* **1961**, *83*, 4076-4083.
- 89) Heusler, K.; Kalvoda, J. "Intramolecular Radical Reactions" *Angew. Chem.* **1964**, *76*, 518-531.
- 90) Majetich, G.; Wheless, K. "Remote Intramolecular Free Radical Functionalizations: An Update" *Tetrahedron* **1995**, *51*, 7095-7129.

- 91) Davis, F. A.; Fang, T.; Chao, B.; Burns, D. M. "Asymmetric Synthesis of the Four Stereoisomers of 4-Hydroxypiperic Acid" *Synthesis* **2000**, 2106-2112.
- 92) Davis, F. A.; Lee, S.; Yan, H.; Titus, D. D. "Asymmetric Synthesis of Quaternary α -Amino Phosphonates Using Sulfinimines" *Org. Lett.* **2001**, 3, 1757-1760.
- 93) Davis, F. A.; Fang, T.; Goswami, R. "Asymmetric Synthesis of Substituted Prolines from Δ -Amino B-Ketoesters. Methyl (2*S*,5*R*)-(+)-5-Phenylpyrrolidine-2-Carboxylate" *Org. Lett.* **2002**, 4, 1599-1602.
- 94) Davis, F. A.; Yang, B.; Deng, J. "Asymmetric Synthesis of Cis-5-Tert-Butylproline with Metal Carbenoid N_H Insertion" *J. Org. Chem.* **2003**, 68, 5147-5152.
- 95) Davis, F. A.; Zhang, Y.; Anilkumar, G. "Asymmetric Synthesis of the Quinolizidine Alkaloid (-)-Epimyrten with Intramolecular Mannich Cyclization and N-Sulfinyl Δ -Amino B-Ketoesters" *J. Org. Chem.* **2003**, 68, 8061-8064.
- 96) Davis, F. A.; Wu, Y.; Xu, H.; Zhang, J. "Asymmetric Synthesis of Cis-5-Substituted Pyrrolidine 2-Phosphonates Using Metal Carbenoid N_H Insertion and Δ -Amino B-Ketophosphonates" *Org. Lett.* **2004**, 6, 4523-4525.
- 97) Dong, C.; Deng, G.; Wang, J. "New Approaches to Polysubstituted Pyrroles and Γ -Lactams Based on Nucleophilic Addition of Ti(IV) Enolates Derived from α -Diazo-B-Keto Carbonyl Compounds to N-Tosylimines" *J. Org. Chem.* **2006**, 71, 5560-5564.
- 98) Zhou, P.; Chen, B.-C.; Davis, F. A. "Recent Advances in Asymmetric Reactions Using Sulfinimines (N-Sulfinyl Imines)" *Tetrahedron* **2004**, 60, 8003-8030.
- 99) Nicolas, E.; Russell, K. C.; Hruby, V. J. "Asymmetric 1,4-Addition of Organocuprates to Chiral α,β -Unsaturated N-Acyl-4-Phenyl-2-Oxazolidinones: A New Approach to the Synthesis of Chiral β -Branched Carboxylic Acids" *J. Org. Chem.* **1993**, 58, 766-770.

- 100) Dambacher, J.; Anness, R.; Pollock, P.; Bergdahl, M. "Highly Diastereoselective Conjugate Additions of Monoorganocopper Reagents to Chiral Imides" *Tetrahedron* **2004**, *60*, 2097-2110.
- 101) Ho, G.-J.; Mathre, D. J. "Lithium-Initiated Imide Formation. A Simple Method for N-Acylation of 2-Oxazolidinones and Bornane-2,10-Sultam" *J. Org. Chem.* **1995**, *60*, 2271-2273.
- 102) Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D. "Diazo Transfer Reactions with P-Acetamidobenzenesulfonyl Azide" *Synth. Commun.* **1987**, *17*, 1709-1716.
- 103) Santos, A. P.; Moreno, P. R. H. "Pilocarpus Spp.: A Survey of Its Chemical Constituents and Biological Activities" *Rev. Bras. Cienc. Farm.* **2004**, *40*, 115-137.
- 104) Hirama, M.; Shigemoto, T.; Ito, S. "Reversal of Diastereofacial Selectivity in the Intramolecular Michael Addition of Δ -Carbamoyloxy-A,B-Unsaturated Esters. Synthesis of N-Benzoyl-D,L-Daunosamine" *Tetrahedron Lett.* **1985**, *26*, 4137-4140.
- 105) Hirama, M.; Shigemoto, T.; Yamazaki, Y.; Ito, S. "Diastereoselective Synthesis of N-Acetyl-D,L-Acosamine and N-Benzoyl-D,L-Ristosamine" *Tetrahedron Lett.* **1985**, *26*, 4133-4136.
- 106) Hirama, M.; Shigemoto, T.; Yamazaki, Y.; Ito, S. "Carbamate-Mediated Functionalization of Unsaturated Alcohols. 3. Intramolecular Michael Addition of O-Carbamates to A,B-Unsaturated Esters. A New Diastereoselective Amination in an Acyclic System" *J. Am. Chem. Soc.* **1985**, *107*, 1797-1798.
- 107) Hirama, M.; Nishizaki, I.; Shigemoto, T.; Ito, S. "New Acyclic Approach to 3-Amino-2,3,6-Trideoxy-L-Hexoses: A Stereocontrolled Synthesis of N-Benzoyl L-Daunosamine" *J. Chem. Soc., Chem. Commun.* **1986**, 393-394.
- 108) Hirama, M.; Shigemoto, T.; Ito, S. "Stereodivergent Total Synthesis of N-Acetylacosamone and N-Benzoylristosamine" *J. Org. Chem.* **1987**, *52*, 3342-3346.

- 109) Song, J.; Hollingsworth, R. I. "Homochiral 4-Hydroxy-5-Hexenoic Acids and Their Derivatives and Homologs from Carbohydrates" *Tetrahedron: Asymmetry* **2001**, *12*, 387-391.
- 110) Wang, D.; Nugent, W. A. "2-Deoxyribose as a Rich Source of Chiral 5-Carbon Building Blocks" *J. Org. Chem.* **2007**, *72*, 7307-7312.
- 111) Swallen, L. C.; Boord, C. E. "The Synthesis of Beta-Bromo-Alkyl Ethers and Their Use in Further Synthesis" *Journal of the American Chemical Society* **1930**, *52*, 651-660.
- 112) Kochi, J. K.; Singleton, D. M. "Stereochemistry of Reductive Elimination by Chromium(Ii) Complexes" *J. Amer. Chem. Soc.* **1968**, *90*, 1582-1589.
- 113) Hanson, J. R. "Applications of Chromium(Ii) Salts in Preparative Organic Chemistry" *Synthesis* **1974**, 1-8.
- 114) Bernet, B.; Vasella, A. "Carbocyclic Compounds from Monosaccharides. I. Transformations in the Glucose Series" *Helv. Chim. Acta* **1979**, *62*, 1990-2016.
- 115) Nakane, M.; Hutchinson, C. R.; Gollman, H. "A Convenient and General Synthesis of 5-Vinylhexofuranosides from 6-Halo-6-Deoxypyranosides" *Tetrahedron Lett.* **1980**, *21*, 1213-1216.
- 116) Fuerstner, A.; Jumbam, D.; Teslic, J.; Weidmann, H. "Metal-Graphite Reagents in Carbohydrate Chemistry. 8. The Scope and Limitations of the Use of Zinc/Silver-Graphite in the Synthesis of Carbohydrate-Derived Substituted Hex-5-Enals and Pent-4-Enals" *J. Org. Chem.* **1991**, *56*, 2213-2217.
- 117) Corey, E. J.; Marfat, A.; Goto, G.; Brion, F. "Leukotriene B. Total Synthesis and Assignment of Stereochemistry" *J. Am. Chem. Soc.* **1980**, *102*, 7984-7985.
- 118) Harcken, C.; Martin, S. F. "Improved E-Selectivity in the Wittig Reaction of Stabilized Ylides with α -Alkoxy Aldehydes and Sugar Lactols" *Org. Lett.* **2001**, *3*, 3591-3593.

- 119) Gunn, B. P.; Brooks, D. W. "Total Synthesis of (\pm)-12-Hydroxy-5,8,14-Cis-10-Trans-Eicosatetraenoic Acid (12-Hete)" *J. Org. Chem.* **1985**, *50*, 4417-4418.
- 120) Corey, E. J.; Clark, D. A.; Goto, G.; Marfat, A.; Mioskowski, C.; Samuelsson, B.; Hammarstroem, S. "Stereospecific Total Synthesis of a "Slow Reacting Substance" of Anaphylaxis, Leukotriene C-1" *J. Am. Chem. Soc.* **1980**, *102*, 1436-1439.
- 121) Torssell, K.; Tyagi, M. P. "Reactions of Parasorbic Acid. Synthesis of 2-Alkoxy-5,6-Dihydro-A-Pyrans and D,L-Osmunda Lactone" *Acta Chem. Scand., Ser. B* **1977**, *B31*, 297-301.
- 122) Chmielewski, M.; Maciejewski, S. "An Approach to B-Lactams from A,B-Unsaturated Sugar Δ -Lactones" *Carbohydr. Res.* **1986**, *157*, C1-C3.
- 123) Maciejewski, S.; Panfil, I.; Belzecki, C.; Chmielewski, M. "An Approach to Carbapenems from A,B-Unsaturated Sugar Lactones" *Tetrahedron* **1992**, *48*, 10363-10376.
- 124) Panfil, I.; Urbanczyk-Lipkowska, Z.; Chmielewski, M. "Isoxazolidin-5-One Analogs of B-Lactam Antibiotics" *Carbohydr. Res.* **1998**, *306*, 505-515.
- 125) Rico, J. G. "Synthesis of Novel B-Amino Acid Precursors: B-Amino-Hydrocoumarins as Unusual Aspartic Acid Mimetics Used in Fibrinogen Receptor Antagonists" *Tetrahedron Lett.* **1994**, *35*, 6599-6602.
- 126) Ono, M.; Zhao, X. Y.; Shida, Y.; Akita, H. " Δ -Lactone Formation from Δ -Hydroxy-Trans-A,B-Unsaturated Carboxylic Acids Accompanied by Trans-Cis Isomerization: Synthesis of (-)-Tetra-O-Acetylosmundalin" *Tetrahedron* **2007**, *63*, 10140-10148.
- 127) Padwa, A.; Dean, D. C.; Osterhout, M. H.; Precado, L.; Semones, M. A. "Synthesis of Functionalized Azomethine Ylides Via the Rh(II)-Catalyzed Cyclization of A-Diazo Carbonyls onto Imino Π -Bonds" *J. Org. Chem.* **1994**, *59*, 5347-5357.

- 128) Li, G.-Y.; Chen, J.; Yu, W.-Y.; Hong, W.; Che, C.-M. "Stereoselective Synthesis of Functionalized Pyrrolidines by Ruthenium Porphyrin-Catalyzed Decomposition of α -Diazo Esters and Cascade Azomethine Ylide Formation/1,3-Dipolar Cycloaddition Reactions" *Org. Lett.* **2003**, *5*, 2153-2156.
- 129) Ko, E. J.; Savage, G. P.; Williams, C. M.; Tsanaktsidis, J. "Reducing the Cost, Smell, and Toxicity of the Barton Reductive Decarboxylation: Chloroform as the Hydrogen Atom Source" *Org. Lett.* **2011**, *13*, 1944-1947.
- 130) House, H. O.; Blankley, C. J. "Preparation and Decomposition of Unsaturated Esters of Diazoacetic Acid" *J. Org. Chem.* **1968**, *33*, 53-60.
- 131) Blankley, C. J.; Sauter, F. J.; House, H. O. "Crotyl Diazoacetate" *Org. Synth.* **1969**, *49*, No pp. given.
- 132) Corey, E. J.; Myers, A. G. "Efficient Synthesis and Intramolecular Cyclopropanation of Unsaturated Diazoacetic Esters" *Tetrahedron Lett.* **1984**, *25*, 3559-3562.
- 134) Neises, B.; Steglich, W. "4-Dialkylaminopyridines as Acylation Catalysts. 5. Simple Method for the Esterification of Carboxylic Acids" *Angew. Chem.* **1978**, *90*, 556-557.
- 135) Neises, B.; Steglich, W. "Esterification of Carboxylic Acids with Dicyclohexylcarbodiimide/4-Dimethylaminopyridine: Tert-Butyl Ethyl Fumarate ((E)-2-Butenedioic Acid, Ethyl 1,1-Dimethylethyl Ester)" *Org. Synth.* **1985**, *63*, 183-187.
- 136) Toma, T.; Shimokawa, J.; Fukuyama, T. "N,N'-Ditosylhydrazine: A Convenient Reagent for Facile Synthesis of Diazoacetates" *Org. Lett.* **2007**, *9*, 3195-3197.
- 137) Velazquez, F.; Olivo, H. F. "Synthesis of Bicyclic Γ -Ylidenetetronates" *Org. Lett.* **2002**, *4*, 3175-3178.
- 138) Willstatter, R.; Bode, A. "Conversion of Tropinone into R-Cocaine" *Ber.* **1901**, *34*, 1457-1461.

- 139) Willstatter, R. "Synthesis of Tropine" *Annalen* **1903**, 326, 23-42.
- 140) Willstatter, R.; Bommer, M. "A Complete Synthesis of DI-Ecgonine and of Tropinone" *Justus Liebigs Ann. Chem.* **1920**, 422, 15-35.
- 141) Robinson, R. "Synthesis of Tropinone" *J. Chem. Soc., Trans.* **1917**, 111, 762-768.
- 142) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley: 1998, 652 pp.
- 143) Aszodi, J.; Rowlands, D. A.; Mauvais, P.; Collette, P.; Bonnefoy, A.; Lampilas, M. "Design and Synthesis of Bridged Γ -Lactams as Analogues of B-Lactam Antibiotics" *Bioorg. Med. Chem. Lett.* **2004**, 14, 2489-2492.
- 144) Overman, L. E. "Application of Intramolecular Heck Reactions for Forming Congested Quaternary Carbon Centers in Complex Molecule Total Synthesis" *Pure Appl. Chem.* **1994**, 66, 1423-1430.
- 145) Link, J. T.; Overman, L. E. "Forming Cyclic Compounds with the Intramolecular Heck Reaction" *CHEMTECH* **1998**, 28, 19-26.
- 146) Link, J. T.; Overman, L. E. **1998**, Intramolecular Heck Reactions in Natural Product Chemistry.
- 147) Ashimori, A.; Overman, L. E. "Catalytic Asymmetric Synthesis of Quaternary Carbon Centers by Intramolecular Heck Reaction. Synthetic Developments and Mechanistic Studies" *Yuki Gosei Kagaku Kyokaishi* **2000**, 58, 718-727.
- 148) Donde, Y.; Overman, L. E. **2000**, Asymmetric Intramolecular Heck Reactions.
- 149) Dounay, A. B.; Overman, L. E. "The Asymmetric Intramolecular Heck Reaction in Natural Product Total Synthesis" *Chem. Rev. (Washington, DC, U. S.)* **2003**, 103, 2945-2963.

- 150) Dounay, A. B.; Overman, L. E. **2009**, The Asymmetric Intramolecular Mizoroki-Heck Reaction in Natural Product Total Synthesis.
- 151) Abelman, M. M.; Oh, T.; Overman, L. E. "Intramolecular Alkene Arylations for Rapid Assembly of Polycyclic Systems Containing Quaternary Centers. A New Synthesis of Spirooxindoles and Other Fused and Bridged Ring Systems" *J. Org. Chem.* **1987**, *52*, 4130-4133.
- 152) Coe, J. W. "Total Synthesis of (\pm)-Cytisine Via the Intramolecular Heck Cyclization of Activated N-Alkyl Glutarimides" *Org. Lett.* **2000**, *2*, 4205-4208.
- 153) Bennasar, M. L.; Zulaica, E.; Sole, D.; Roca, T.; Garcia-Diaz, D.; Alonso, S. "Total Synthesis of the Bridged Indole Alkaloid Apparicine" *J. Org. Chem.* **2009**, *74*, 8359-8368.
- 154) Grigg, R.; Sridharan, V.; York, M. "Sequential and Cascade Olefin Metathesis-Intramolecular Heck Reaction" *Tetrahedron Lett.* **1998**, *39*, 4139-4142.
- 155) Grigg, R.; York, M. "Bimetallic Catalytic Cascade Ring-Closing Metathesis-Intramolecular Heck Reactions Using a Fluorous Biphasic Solvent System or a Polymer-Supported Palladium Catalyst" *Tetrahedron Lett.* **2000**, *41*, 7255-7258.
- 156) Sahn, J. J.; Su, J. Y.; Martin, S. F. "Facile and Unified Approach to Skeletally Diverse, Privileged Scaffolds" *Org. Lett.* **2011**, *13*, 2590-2593.
- 157) Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. "Enantioselective Total Syntheses of Ircinal a and Related Manzamine Alkaloids" *J. Am. Chem. Soc.* **1999**, *121*, 866-867.
- 158) Humphrey, J. M.; Liao, Y.; Ali, A.; Rein, T.; Wong, Y.-L.; Chen, H.-J.; Courtney, A. K.; Martin, S. F. "Enantioselective Total Syntheses of Manzamine a and Related Alkaloids" *J. Am. Chem. Soc.* **2002**, *124*, 8584-8592.
- 159) Neipp, C. E.; Martin, S. F. "A Ring-Closing Olefin Metathesis Approach to Bridged Azabicyclic Structures" *Tetrahedron Lett.* **2002**, *43*, 1779-1782.

- 160) Neipp, C. E. I. The Synthesis of Homoallylic Amines Via a 1,2-Metalate Rearrangement. II. The Synthesis of Bridged Azabicyclic Structures Via Ring-Closing Olefin Metathesis. Dissertation, 2003.
- 161) Neipp, C. E.; Martin, S. F. "Synthesis of Bridged Azabicyclic Structures Via Ring-Closing Olefin Metathesis" *J. Org. Chem.* **2003**, 68, 8867-8878.
- 162) Kuznetsov, N. Y.; Khrustalev, V. N.; Godovikov, I. A.; Bubnov, Y. N. "Synthesis of Bridged Azabicycles from Pyridines and Pyrrole by a Diallylboration-Ring Closing Metathesis Sequence" *Eur. J. Org. Chem.* **2005**, 113-120.
- 163) Bubnov, Y. N.; Kuznetsov, N. Y.; Gurskii, M. E.; Semenova, A. L.; Kolomnikova, G. D.; Potapova, T. V. "Construction of Nitrogen Bicyclic and Cage Compounds with the Use of Allylic Organoboranes" *Pure Appl. Chem.* **2006**, 78, 1357-1368.
- 164) Itoh, T.; Yamazaki, N.; Kibayashi, C. "Asymmetric Synthesis of (-)-Adaline" *Org. Lett.* **2002**, 4, 2469-2472.
- 165) Brenneman, J. B.; Martin, S. F. "Application of Intramolecular Enyne Metathesis to the Synthesis of Aza[4.2.1]Bicyclics: Enantiospecific Total Synthesis of (+)-Anatoxin-A" *Org. Lett.* **2004**, 6, 1329-1331.
- 166) Mori, M.; Tomita, T.; Kita, Y.; Kitamura, T. "Synthesis of (+)-Anatoxin-a Using Enyne Metathesis" *Tetrahedron Lett.* **2004**, 45, 4397-4399.
- 167) Aggarwal, V. K.; Astle, C. J.; Rogers-Evans, M. "A Concise Asymmetric Route to the Bridged Bicyclic Tropane Alkaloid Ferruginine Using Enyne Ring-Closing Metathesis" *Org. Lett.* **2004**, 6, 1469-1471.
- 168) Miller, K. A.; Shanahan, C. S.; Martin, S. F. "The Pauson-Khand Reaction as a New Entry to the Synthesis of Bridged Bicyclic Heterocycles: Application to the Enantioselective Total synthesis of (-)-Alstonerine" *Tetrahedron* **2008**, 64, 6884-6900.

- 169) Lohse, A.; Ernholz, B. V.; Bols, M. "Synthesis of Substituted Chiral Piperazines Resembling Aza-Sugars" *Acta Chem. Scand.* **1998**, 52, 499-502.
- 170) Berkheij, M.; van, d. S. L.; Sewing, C.; den, B. D. J.; Terpstra, J. W.; Hiemstra, H.; Iwema, B. W. I.; van, d. H. A.; van, M. J. H. "Synthesis of 2-Substituted Piperazines Via Direct α -Lithiation" *Tetrahedron Lett.* **2005**, 46, 2369-2371.
- 171) Wilkinson, T. J.; Stehle, N. W.; Beak, P. "Enantioselective Syntheses of 2-Alkyl- and 2,6-Dialkylpiperidine Alkaloids: Preparations of the Hydrochlorides of (-)-Coniine, (-)-Solenopsin a, and (-)-Dihydropinidine" *Org. Lett.* **2000**, 2, 155-158.

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